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(54) Title: NOVEL TETRACYCLINE DERIVATIVES (57) Abstract The present invention relates to novel tetracycline derivatives, to intermediates used in their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in the prevention, treatment or control of bacterial infections in warm-blooded animals.		

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NOVEL TETRACYCLINE DERIVATIVESBackground of the Invention

The present invention relates to novel tetracycline derivatives, to intermediates used in their preparation, to pharmaceutical compositions containing them and to their medicinal use.

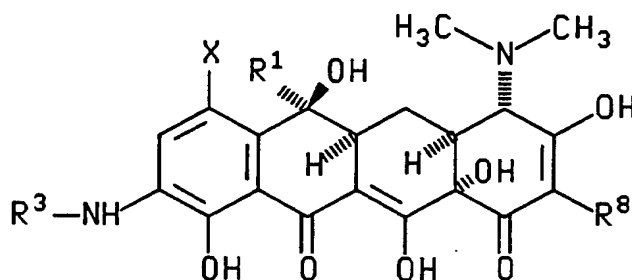
10 European Patent Publication 618,190, published October 5, 1994, refers to 9-[(substituted glycyloamido]-6-(substituted)-5-hydroxy-6-deoxytetracyclines, methods for their production and methods of using the active agents for the prevention, treatment or control of bacterial infections in warm-blooded animals.

15 European Patent Publication 536,515, published April 14, 1993, refers to 7-substituted-9-(substituted amino)-6-demethyl-6-deoxytetracyclines, methods for their production and methods of using the active agents for the prevention, treatment or control of bacterial infections in warm-blooded animals.

Summary of the Invention

The present invention relates to compounds of the formula

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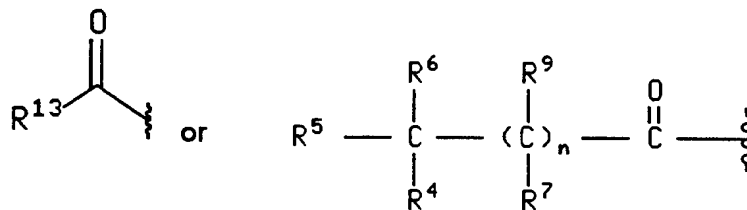
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wherein X is hydrogen;

R¹ is methyl;

R³ is a group of the formula



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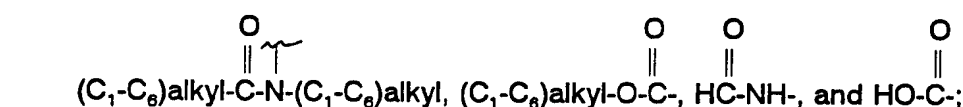
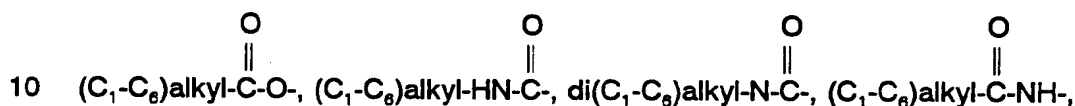
wherein n is an integer from zero to four;

R⁴ is hydrogen or (C₁-C₆)alkyl;

R⁵ is hydrogen; (C₁-C₆)alkyl optionally substituted with one or more substituents, preferably one to three substituents, independently selected from

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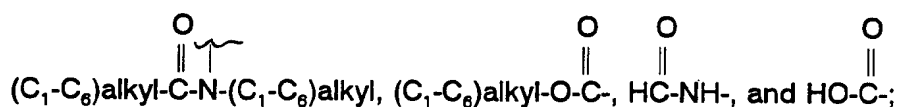
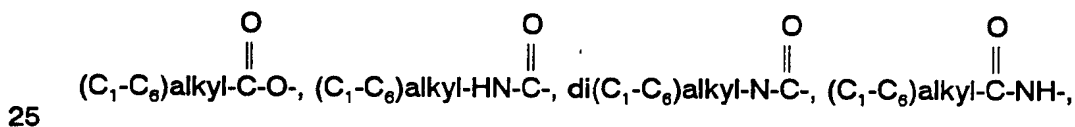
methylthio, (C₁-C₆)alkoxy, amino, guanidino, amido, carboxamido,



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(C₆-C₁₀)aryl-(CH₂)_h-, wherein h is an integer from zero to three, wherein the (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl-(CH₂)_h group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl,

20 amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



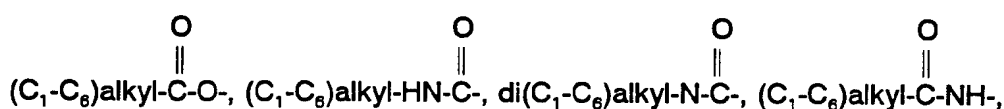
30 or (C₃-C₆)cycloalkyl-(CH₂)_j-, wherein j is an integer from zero to three, wherein the (C₃-C₆)cycloalkyl moiety of said (C₃-C₆)cycloalkyl-(CH₂)_j- group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-

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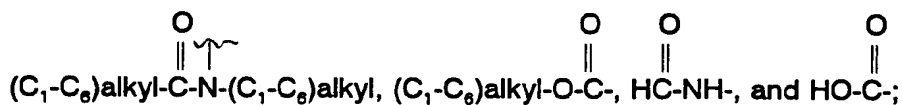
C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-

C₆)alkylamino, amido, carboxamido,

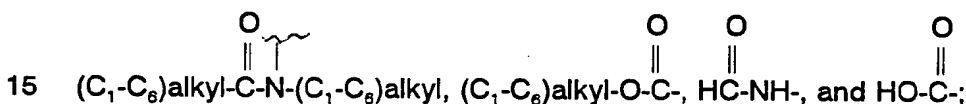
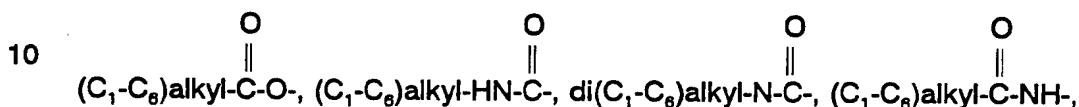
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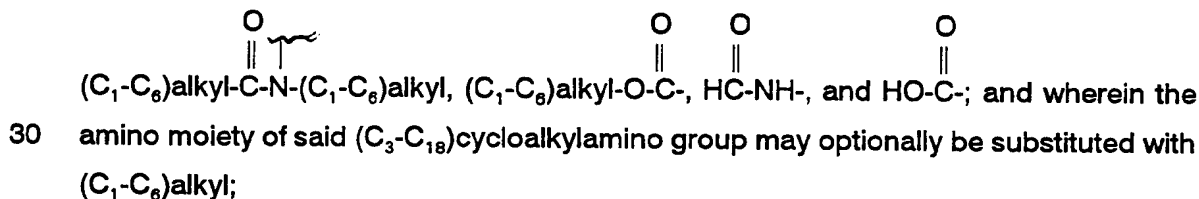
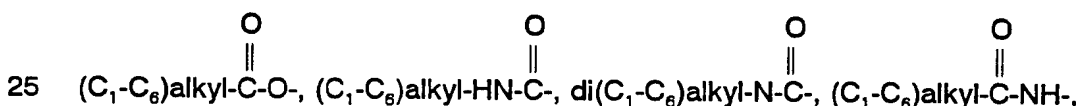
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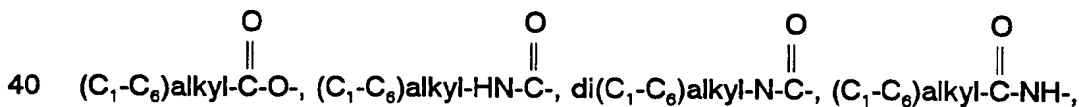
R^8 is halogen; amino; hydroxylamino; (C_1-C_{12}) alkylamino optionally substituted
 5 with one or more substituents, preferably one to three substituents, independently
 selected from halogen, hydroxy, (C_1-C_6) alkoxy, (C_1-C_6) alkylsulfonyl, trihalo (C_1-C_6) alkyl,
 amino, cyano, (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, amido, carboxamido,



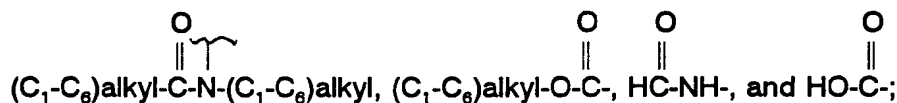
(C_3-C_{18}) cycloalkylamino wherein the (C_3-C_{18}) cycloalkyl moiety of said $(C_3-$
 $C_{18})$ cycloalkyl amino group may optionally be substituted with one or more
 substituents, preferably one to three substituents, independently selected from
 halogen, hydroxy, (C_1-C_6) alkoxy, (C_1-C_6) alkylsulfonyl, trihalo (C_1-C_6) alkyl, amino, cyano,
 20 (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, amido, carboxamido, (C_1-C_6) alkyl,



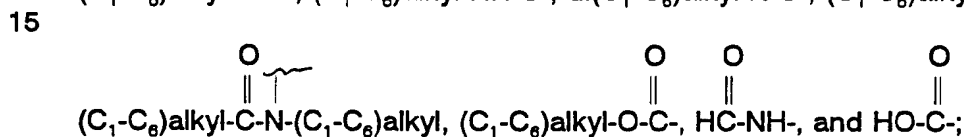
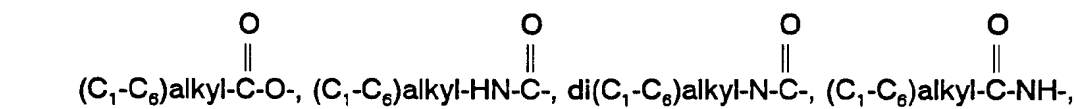
di (C_3-C_{18}) cycloalkyl-amino optionally substituted with one or more substituents,
 preferably one to three substituents, independently selected from halogen, hydroxy,
 (C_1-C_6) alkoxy, (C_1-C_6) alkylsulfonyl, trihalo (C_1-C_6) alkyl, amino, cyano, (C_1-C_6) alkylamino,
 35 di (C_1-C_6) alkylamino, amido, carboxamido, (C_1-C_6) alkyl,



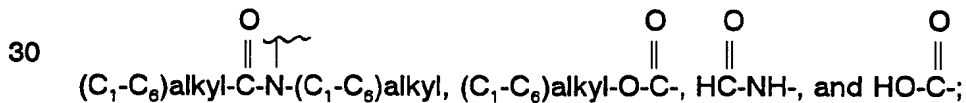
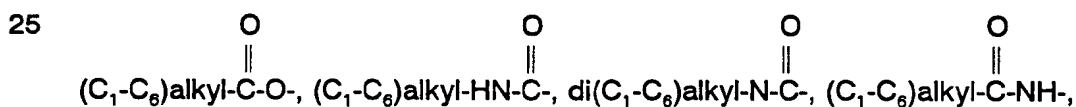
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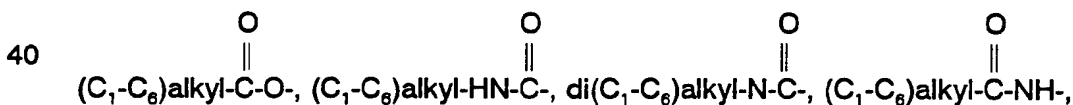
- (C₆-C₁₀)aryl-(CH₂)_m-amino, wherein m is an integer from zero to three, wherein
- 5 the (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl-(CH₂)_m-amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido,
- 10 carboxamido, (C₁-C₆)alkyl,



- di(C₁-C₆)alkyl-amino optionally substituted with one or more substituents,
- 20 preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

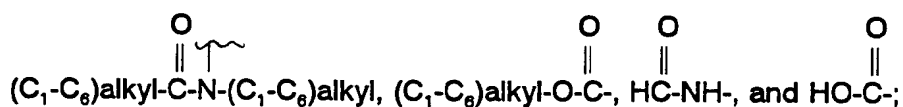


- (C₂-C₁₀)azacycloalkyl optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano,
- 35 (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

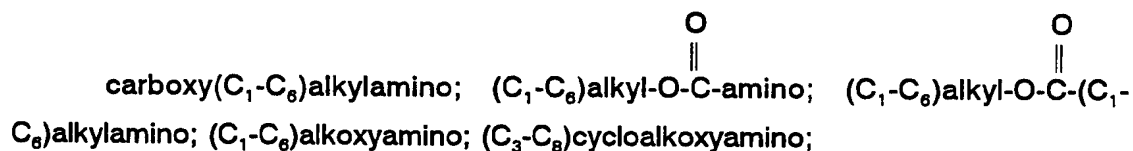


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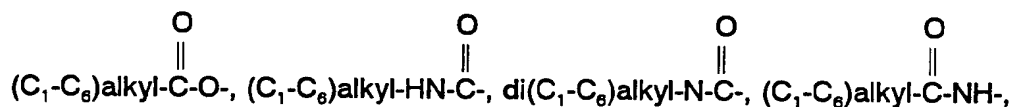


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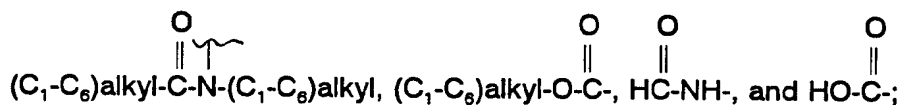


10 $(C_6-C_{10})\text{aryl}-(\text{CH}_2)_t\text{-oxyamino}$, wherein t is an integer from zero to three, wherein the $(C_6-C_{10})\text{aryl}$ moiety of said $(C_6-C_{10})\text{aryl}-(\text{CH}_2)_t\text{-oxyamino}$ group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, $(C_1-C_6)\text{alkoxy}$, trihalo $(C_1-C_6)\text{alkyl}$, amino, cyano, $(C_1-C_6)\text{alkylamino}$, hydroxy, $(C_1-C_6)\text{alkyl}$, $(C_1-C_6)\text{alkylsulfonyl}$, di $(C_1-C_6)\text{alkylamino}$, amido, carboxamido,

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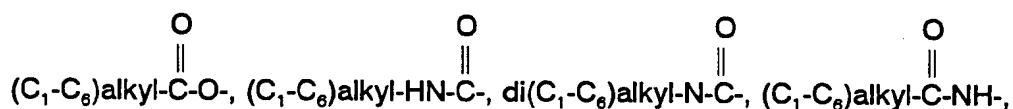
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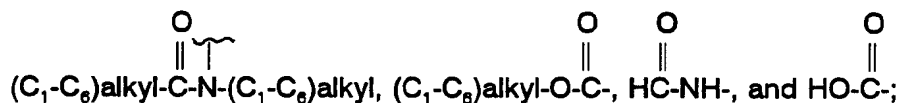
or a heterocycle- $(\text{CH}_2)_k\text{-amino}$ group, wherein k is an integer from zero to three, wherein said heterocycle is selected from pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolyl and benzoxazinyl;

wherein the heterocycle moiety of said heterocycle- $(\text{CH}_2)_k\text{-}$ group may be, where possible, substituted with from one to three substituents independently selected from $(C_1-C_6)\text{alkyl}$, halogen, hydroxy, cyano, $(C_1-C_6)\text{alkoxy}$, $(C_1-C_6)\text{alkylsulfonyl}$, trihalo $(C_1-C_6)\text{alkyl}$, amino, $(C_1-C_6)\text{alkylamino}$, di $(C_1-C_6)\text{alkylamino}$, amido, carboxamido,

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5 or R⁵ and R⁶ taken together may form a $-(CH_2)_pW(CH_2)_q-$ ring wherein W is

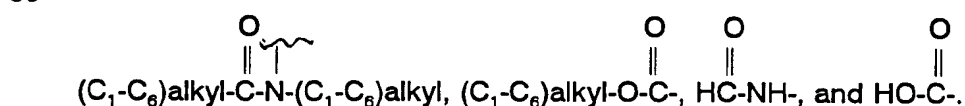
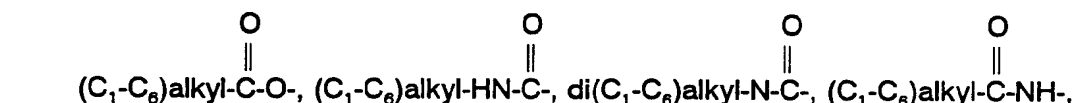
selected from $-\overset{\text{O}}{\parallel}\text{N}-(C_1-C_3)\text{alkyl}-CH_2-$, $-\overset{\text{O}}{\parallel}\text{NH}$, O, S, and $-\overset{\text{O}}{\parallel}\text{NOB}$; wherein B is selected from hydrogen and $(C_1-C_3)\text{alkyl}$, p is an integer from one to three, and q is an integer from one to three;

- 10 R⁷ is hydrogen or $(C_1-C_6)\text{alkyl}$;
 R⁸ is $-\text{CONH}_2$ or $-\text{CONHCH}_2-\text{NR}^{11}\text{R}^{12}$;
 R⁹ is hydrogen or $(C_1-C_6)\text{alkyl}$;
 R¹¹ is $(C_1-C_6)\text{alkyl}$;
 R¹² is $(C_1-C_6)\text{alkyl}$; or

15 R¹¹ and R¹² taken together form a $-(CH_2)_r-Y-(CH_2)_s$ ring wherein Y is $-\overset{\text{O}}{\parallel}\text{N}-(C_1-$

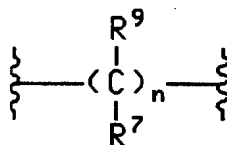
$C_3)\text{alkyl}$, $-CH_2-$, $-\text{NH}$, oxygen, sulfur or $-\text{NOB}$; wherein B is selected from hydrogen or
 20 $(C_1-C_3)\text{alkyl}$, r is an integer from one to three, and s is an integer from one to three;

R¹³ is hydrogen, $(C_1-C_6)\text{alkoxy}$, $(C_1-C_6)\text{alkyl}$, $(C_1-C_6)\text{alkoxy}$, $(C_3-C_6)\text{cycloalkyl}$, $(C_3-C_6)\text{cycloalkylmethyl}$, or $(C_6-C_{10})\text{aryl}$ optionally substituted with one or more substituents, preferably one to three substituents, independently selected from fluoro, hydroxy, $(C_1-C_6)\text{alkoxy}$, trihalo $(C_1-C_6)\text{alkyl}$, amino, cyano, $(C_1-C_6)\text{alkylamino}$,
 25 di $(C_1-C_6)\text{alkylamino}$, amido, carboxamido,



The moiety

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as used herein refers to a variable length carbon chain in which each carbon atom of the chain may optionally be independently substituted with one or both of the moieties R^7 and R^8 .

The present invention also relates to the pharmaceutically acceptable acid
5 addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of those compounds of formula I that are basic in nature are those which form non-toxic acid addition salts, e.g., salts containing pharmacologically acceptable anions, such as the chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid
10 citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [e.g., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

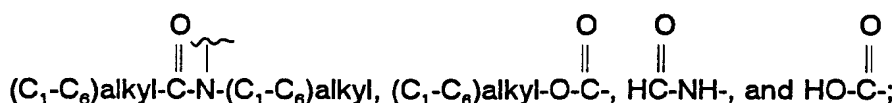
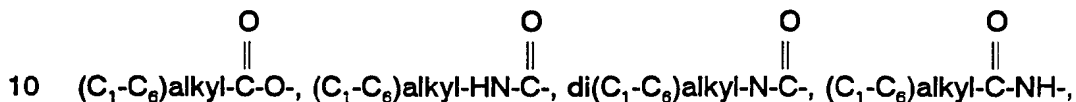
The invention also relates to base addition salts of formula I. The chemical
bases that may be used as reagents to prepare pharmaceutically acceptable base salts
15 of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to, those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-
20 methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

Preferred compounds of the invention are compounds of the formula I wherein R^8 is $-\text{CONH}_2$.

More preferred compounds of the formula I are those wherein n is zero; R^4 is
25 hydrogen; and R^5 is hydrogen.

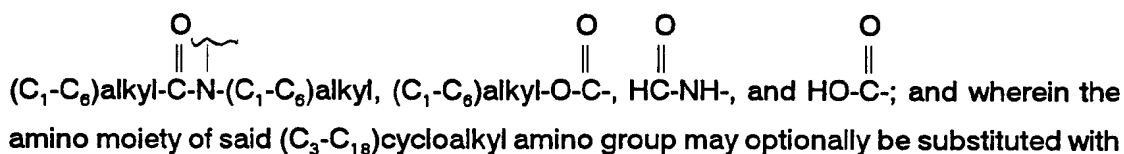
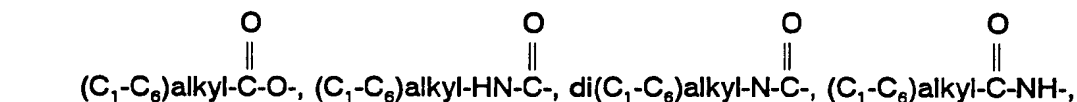
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Most preferred compounds of the formula I are those wherein R⁶ is halogen, amino, hydroxylamino, (C₁-C₁₂)alkylamino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



15 (C₃-C₁₈)cycloalkylamino wherein the (C₃-C₁₈)cycloalkyl moiety of said (C₃-C₁₈)cycloalkyl amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano,

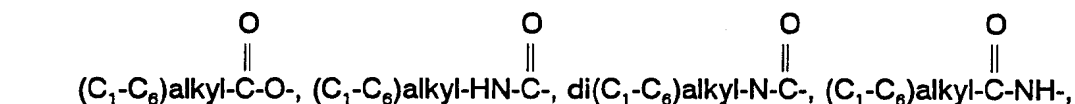
20 (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido, (C₁-C₆)alkyl,



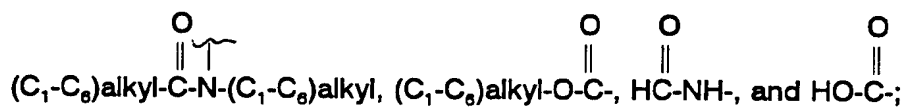
30 (C₁-C₆)alkyl;

di(C₁-C₆)alkyl-amino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-

35 C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

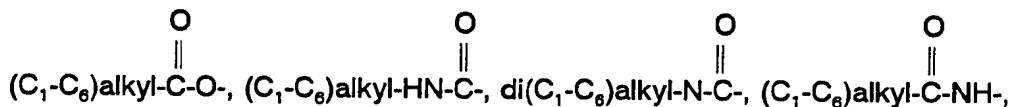


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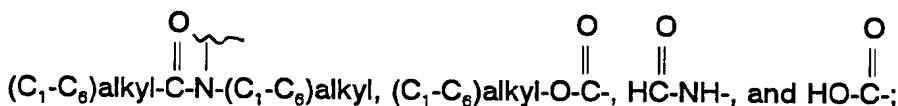


(C₂-C₁₀)azacycloalkyl optionally substituted with one or more substituents,
 5 preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-
 C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano,
 (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

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15



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or R⁵ and R⁶ taken together may form a -(CH₂)_pW(CH₂)_q- ring wherein W is

selected from $\text{N}-(C_1-C_3)\text{alkyl}$, -CH₂-, -NH-, O, S, and -NOB; wherein B is selected from
 hydrogen and (C₁-C₃)alkyl, p is an integer from one to three, and q is an integer from
 25 one to three.

The following compounds of formula I are particularly preferred:

9-[(N,N-dimethylaminoacetyl)amino]tetracycline;

9-[(tert-butylaminoacetyl)amino]tetracycline;

9-[(N-methyl-N'-tert-butylaminoacetyl)amino]tetracycline;

30 9-[(diisopropylaminoacetyl)amino]tetracycline;

9-[(pyrrolidinoacetyl)amino]tetracycline;

9-[(cycloheptylaminoacetyl)amino]tetracycline; and

9-[(tert-amylaminoacetyl)amino]tetracycline.

Other compounds of the invention include:

35 9-[(n-butylaminoacetyl)amino]tetracycline;

9-[(isopropylaminoacetyl)amino]tetracycline;

9-[(n-pentylaminoacetyl)amino]tetracycline;

9-[(piperidinoacetyl)amino]tetracycline;

9-[(azetidinoacetyl)amino]tetracycline;

40 9-[(n-hexylaminoacetyl)amino]tetracycline;

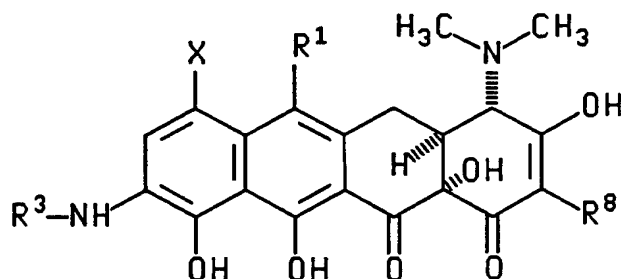
-10-

- 9-[(cyclohexylaminoacetyl)amino]tetracycline;
9-[(N-methyl-n-butylaminoacetyl)amino]tetracycline;
9-[(3-ethoxypropylaminoacetyl)amino]tetracycline;
9-[(3-dimethylaminopropylaminoacetyl)amino]tetracycline;
5 9-[(diethylaminoacetyl)amino]tetracycline;
9-[(cyclopentylaminoacetyl)amino]tetracycline;
9-[(hexylaminoacetyl)amino]tetracycline;
9-[(1-methylpiperazineacetyl)amino]tetracycline;
9-[(cyclobutylaminoacetyl)amino]tetracycline;
10 9-[(homopiperidinoacetyl)amino]tetracycline;
9-[(methylcyclopropylaminoacetyl)amino]tetracycline;
9-[(ethylaminoacetyl)amino]tetracycline;
9-[(3-methoxypropylaminoacetyl)amino]tetracycline;
9-[(methylaminoacetyl)amino]tetracycline;
15 9-[(isoamylaminoacetyl)amino]tetracycline;
9-[(N-ethylisopropylaminoacetyl)amino]tetracycline;
9-[(benzylaminoacetyl)amino]tetracycline;
9-[(diisobutylaminoacetyl)amino]tetracycline;
9-[(N-methylcyclohexylaminoacetyl)amino]tetracycline;
20 9-[(N-methylisopropylaminoacetyl)amino]tetracycline;
9-[(cyclooctylaminoacetyl)amino]tetracycline;
9-[(cyclopropylaminoacetyl)amino]tetracycline;
9-[(isobutylaminoacetyl)amino]tetracycline;
9-[(para-trifluoromethylbenzylaminoacetyl)amino]tetracycline;
25 9-[(N-methylethylaminoacetyl)amino]tetracycline;
9-[(N-methylpropylaminoacetyl)amino]tetracycline;
9-[(N-ethylbutylaminoacetyl)amino]tetracycline;
9-[(N-ethylcyclohexylaminoacetyl)amino]tetracycline;
9-[(glycylacetyl)amino]tetracycline;
30 9-[(L-alanylacetyl)amino]tetracycline;
9-[(L-valylacetyl)amino]tetracycline;
9-[(L-phenylalanylacetyl)amino]tetracycline;
9-[(L-glutamylacetyl)amino]tetracycline;

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9-[(D-alanylacetyl)amino]tetracycline;
 9-[(D-valylacetyl)amino]tetracycline;
 9-[(D-phenylalanylacetyl)amino]tetracycline;
 9-[(D-glutamylacetyl)amino]tetracycline;
 5 9-(L-alanylamino)tetracycline;
 9-(L-valylamino)tetracycline;
 9-(L-phenylalanylamino)tetracycline;
 9-(L-glutamylamino)tetracycline;
 9-(D-alanylamino)tetracycline;
 10 9-(D-valylamino)tetracycline;
 9-(D-phenylalanylamino)tetracycline; and
 9-(D-glutamylamino)tetracycline.

The present invention also relates to compounds of the formula



II

wherein X is hydrogen or chlorine, R¹ is hydrogen or methyl, and R³, R⁴, R⁵, R⁶,
 25 R⁷, R⁸, R⁹, R¹¹, R¹² and R¹³ are as defined above for formula I. These compounds are
 useful as antibiotics.

The present invention also relates to the pharmaceutically acceptable acid
 addition salts of compounds of the formula II. The acids which are used to prepare the
 pharmaceutically acceptable acid addition salts of those compounds of formula II that
 30 are basic in nature are those which form non-toxic acid addition salts, e.g., salts
 containing pharmacologically acceptable anions, such as the chloride, bromide, iodide,
 nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid
 citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate,

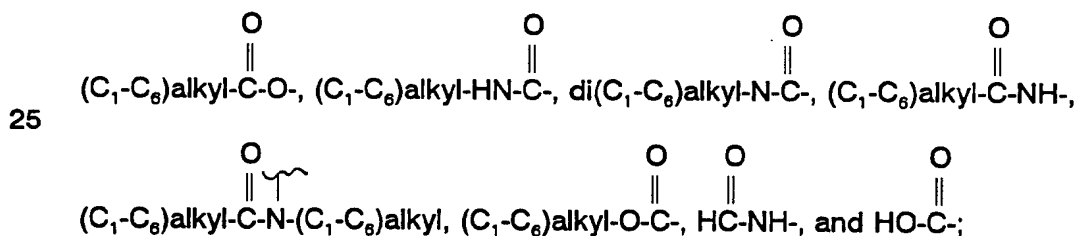
benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [e.g., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The invention also relates to base addition salts of formula II. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to, those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

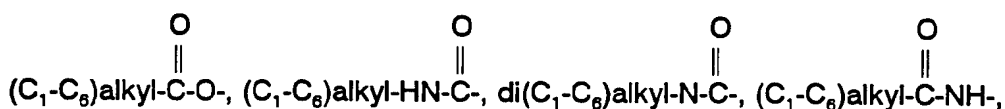
Preferred compounds of formula II are those wherein R⁶ is -CONH₂.

More preferred compounds of the formula II are those wherein n is zero; R⁴ is hydrogen; and R⁵ is hydrogen.

Most preferred compounds of the formula II are those wherein R⁶ is halogen, amino, hydroxylamino, (C₁-C₁₂)alkylamino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



(C₃-C₁₈)cycloalkylamino wherein the (C₃-C₁₈)cycloalkyl moiety of said (C₃-C₁₈)cycloalkyl amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido, (C₁-C₆)alkyl,



-13-

$$(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-N-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl, (C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{O}-\overset{\overset{O}{\parallel}}{C}-, HC-\overset{\overset{O}{\parallel}}{NH}-, \text{ and } HO-\overset{\overset{O}{\parallel}}{C}-;$$
 and wherein the amino moiety of said (C_3-C_{18}) cycloalkyl amino group may optionally be substituted with

5 $(C_1-C_6)alkyl$;
 $di(C_1-C_6)alkyl$ -amino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, $(C_1-C_6)alkylsulfonyl$, trihalo $(C_1-C_6)alkyl$, amino, cyano, $(C_1-C_6)alkylamino$, $di(C_1-C_6)alkylamino$, amido, carboxamido,

10 $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-O-$, $(C_1-C_6)alkyl-HN-\overset{\overset{O}{\parallel}}{C}-$, $di(C_1-C_6)alkyl-N-\overset{\overset{O}{\parallel}}{C}-$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-NH-$,
 15 $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-N-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{O}-\overset{\overset{O}{\parallel}}{C}-$, $HC-\overset{\overset{O}{\parallel}}{NH}-$, and $HO-\overset{\overset{O}{\parallel}}{C}-$;
 $(C_2-C_{10})azacycloalkyl$ optionally substituted with one or more substituents,

20 preferably one to three substituents, independently selected from halogen, hydroxy, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, $(C_1-C_6)alkylsulfonyl$, trihalo $(C_1-C_6)alkyl$, amino, cyano, $(C_1-C_6)alkylamino$, $di(C_1-C_6)alkylamino$, amido, carboxamido,

25 $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-O-$, $(C_1-C_6)alkyl-HN-\overset{\overset{O}{\parallel}}{C}-$, $di(C_1-C_6)alkyl-N-\overset{\overset{O}{\parallel}}{C}-$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-NH-$,
 30 $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-N-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{O}-\overset{\overset{O}{\parallel}}{C}-$, $HC-\overset{\overset{O}{\parallel}}{NH}-$, and $HO-\overset{\overset{O}{\parallel}}{C}-$;
 35

or R^5 and R^6 taken together may form a $-(CH_2)_pW(CH_2)_q-$ ring wherein W is

selected from $-N(C_1-C_3)alkyl-$, $-CH_2-$, $-NH-$, O, S, and $-NOB$; wherein B is selected from
 40 hydrogen and $(C_1-C_3)alkyl$, p is an integer from one to three, and q is an integer from one to three.

The following compounds of formula II are particularly preferred:

9-[(N,N-dimethylaminoacetyl)amino]anhydrotetracycline;

- 9-[(tert-butylaminoacetyl)amino]anhydrotetracycline;
9-[(N-methyl-N'-tert-butylaminoacetyl)amino]anhydrotetracycline;
9-[(diisopropylaminoacetyl)amino]anhydrotetracycline;
9-[(pyrrolidinoacetyl)amino]anhydrotetracycline;
5 9-[(cycloheptylaminoacetyl)amino]anhydrotetracycline; and
9-[(tert-amylaminoacetyl)amino]anhydrotetracycline.
Other compounds of formula II of the invention include:
9-[(bromoacetyl)amino]anhydrotetracycline;
9-[(chloroacetyl)amino]anhydrotetracycline;
10 9-[(N,N-dimethylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(tert-butylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(N-methyl-N'-tert-butylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
15 9-[(diisopropylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(pyrrolidinoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(cycloheptylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(tert-amylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(N,N-dimethylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(tert-butylaminoacetyl)amino]-6-demethylanhydrotetracycline;
20 9-[(N-methyl-N'-tert-butylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(diisopropylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(pyrrolidinoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(cycloheptylaminoacetyl)amino]-6-demethylanhydrotetracycline; and
9-[(tert-amylaminoacetyl)amino]-6-demethylanhydrotetracycline.
25 9-[(n-butylaminoacetyl)amino]anhydrotetracycline;
9-[(isopropylaminoacetyl)amino]anhydrotetracycline;
9-[(n-pentylaminoacetyl)amino]anhydrotetracycline;
9-[(piperidinoacetyl)amino]anhydrotetracycline;
9-[(azetidinoacetyl)amino]anhydrotetracycline;
30 9-[(n-hexylaminoacetyl)amino]anhydrotetracycline;
9-[(cyclohexylaminoacetyl)amino]anhydrotetracycline;
9-[(N-methyl-n-butylaminoacetyl)amino]anhydrotetracycline;
9-[(3-ethoxypropylaminoacetyl)amino]anhydrotetracycline;

- 9-[(3-dimethylaminopropylaminoacetyl)amino]anhydrotetracycline;
9-[(diethylaminoacetyl)amino]anhydrotetracycline;
9-[(cyclopentylaminoacetyl)amino]anhydrotetracycline;
9-[(hexylaminoacetyl)amino]anhydrotetracycline;
5 9-[(1-methylpiperazineacetyl)amino]anhydrotetracycline;
9-[(cyclobutylaminoacetyl)amino]anhydrotetracycline;
9-[(homopiperidinoacetyl)amino]anhydrotetracycline;
9-[(methylcyclopropylaminoacetyl)amino]anhydrotetracycline;
9-[(ethylaminoacetyl)amino]anhydrotetracycline;
10 9-[(3-methoxypropylaminoacetyl)amino]anhydrotetracycline;
9-[(methylaminoacetyl)amino]anhydrotetracycline;
9-[(isoamylaminoacetyl)amino]anhydrotetracycline;
9-[(N-ethylisopropylaminoacetyl)amino]anhydrotetracycline;
9-[(benzylaminoacetyl)amino]anhydrotetracycline;
15 9-[(diisobutylaminoacetyl)amino]anhydrotetracycline;
9-[(N-methylcyclohexylaminoacetyl)amino]anhydrotetracycline;
9-[(N-methylisopropylaminoacetyl)amino]anhydrotetracycline;
9-[(cyclooctylaminoacetyl)amino]anhydrotetracycline;
9-[(cyclopropylaminoacetyl)amino]anhydrotetracycline;
20 9-[(isobutylaminoacetyl)amino]anhydrotetracycline;
9-[(para-trifluoromethylbenzylaminoacetyl)amino]anhydrotetracycline;
9-[(N-methylethylaminoacetyl)amino]anhydrotetracycline;
9-[(N-methylpropylaminoacetyl)amino]anhydrotetracycline;
9-[(N-ethylbutylaminoacetyl)amino]anhydrotetracycline;
25 9-[(N-ethylcyclohexylaminoacetyl)amino]anhydrotetracycline;
9-[(N,N-dimethylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(t-butylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(n-butylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(isopropylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
30 9-[(n-pentylaminoacetyl)amino]amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(piperidinoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(azetidinoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(n-hexylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;

- 9-[(pyrrolidinoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(cyclohexylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(cycloheptylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(N-methyl-n-butylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
5 9-[(N-methyl-t-butylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(3-ethoxypropylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(tert-amylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(3-dimethylaminopropylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
10 9-[(diethylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(cyclopentylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(hexylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(1-methylpiperazineacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(cyclobutylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
15 9-[(homopiperidinoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(methylcyclopropylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(ethylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(3-methoxypropylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
20 9-[(methylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(isoamylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(N-ethylisopropylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(benzylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(diisopropylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
25 9-[(diisobutylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(N-methylcyclohexylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(N-methylisopropylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
30 9-[(cyclooctylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(cyclopropylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(isobutylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;

- 9-[(para-trifluoromethylbenzylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
- 5 9-[(N-methylethylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(N-methylpropylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(N-ethylbutylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(N-ethylcyclohexylaminoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(N,N-dimethylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(t-butylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(n-butylaminoacetyl)amino]-6-demethylanhydrotetracycline;
- 10 9-[(isopropylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(n-pentylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(piperidinoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(azetidinoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(n-hexylaminoacetyl)amino]-6-demethylanhydrotetracycline;
- 15 9-[(pyrrolidinoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(cyclohexylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(cycloheptylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(N-methyl-n-butylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(N-methyl-t-butylaminoacetyl)amino]-6-demethylanhydrotetracycline;
- 20 9-[(3-ethoxypropylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(tert-amylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(3-dimethylaminopropylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(diethylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(cyclopentylaminoacetyl)amino]-6-demethylanhydrotetracycline;
- 25 9-[(hexylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(1-methylpiperazineacetyl)amino]-6-demethylanhydrotetracycline;
9-[(cyclobutylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(homopiperidinoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(methylcyclopropylaminoacetyl)amino]-6-demethylanhydrotetracycline;
- 30 9-[(ethylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(3-methoxypropylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(methylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(isoamylaminoacetyl)amino]-6-demethylanhydrotetracycline;

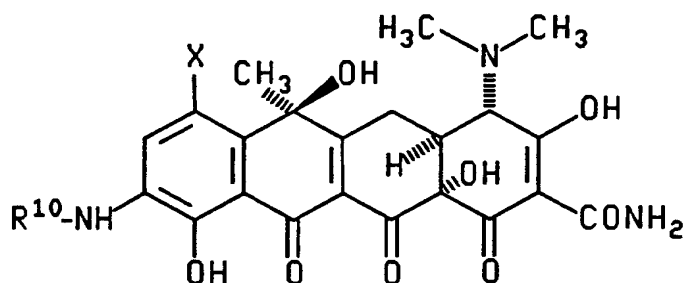
- 9-[(N-ethylisopropylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(benzylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(diisopropylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(diisobutylaminoacetyl)amino]-6-demethylanhydrotetracycline;
5 9-[(N-methylcyclohexylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(N-methylisopropylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(cyclooctylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(cyclopropylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(isobutylaminoacetyl)amino]-6-demethylanhydrotetracycline;
10 9-[(para-trifluoromethylbenzylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(N-methylethylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(N-methylpropylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(N-ethylbutylaminoacetyl)amino]-6-demethylanhydrotetracycline;
9-[(N-ethylcyclohexylaminoacetyl)amino]-6-demethylanhydrotetracycline
15 9-[(glycylacetyl)amino]anhydrotetracycline;
9-[(L-alanylacetyl)amino]anhydrotetracycline;
9-[(L-valylacetyl)amino]anhydrotetracycline;
9-[(L-phenylalanylacetyl)amino]anhydrotetracycline;
9-[(L-glutamylacetyl)amino]anhydrotetracycline;
20 9-[(D-alanylacetyl)amino]anhydrotetracycline;
9-[(D-valylacetyl)amino]anhydrotetracycline;
9-[(D-phenylalanylacetyl)amino]anhydrotetracycline;
9-[(D-glutamylacetyl)amino]anhydrotetracycline;
9-(L-alanylamino)anhydrotetracycline
25 9-(L-valylamino)anhydrotetracycline;
9-(L-phenylalanylamino)anhydrotetracycline;
9-(L-glutamylamino)anhydrotetracycline;
9-(D-alanylamino)anhydrotetracycline
9-(D-valylamino)anhydrotetracycline;
30 9-(D-phenylalanylamino)anhydrotetracycline;
9-(D-glutamylamino)anhydrotetracycline;
9-[(glycylacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
9-[(L-alanylacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;

- 9-[(L-valylacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
 9-[(L-phenylalanylacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
 9-[(L-glutamylacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
 9-[(D-alanylacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
 5 9-[(D-valylacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
 9-[(D-phenylalanylacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
 9-[(D-glutamylacetyl)amino]-7-chloro-6-demethylanhydrotetracycline;
 9-(L-alanylamino)-7-chloro-6-demethylanhydrotetracycline
 9-(L-valylamino)-7-chloro-6-demethylanhydrotetracycline;
 10 9-(L-phenylalanylamino)-7-chloro-6-demethylanhydrotetracycline;
 9-(L-glutamylamino)-7-chloro-6-demethylanhydrotetracycline;
 9-(D-alanylamino)-7-chloro-6-demethylanhydrotetracycline
 9-(D-valylamino)-7-chloro-6-demethylanhydrotetracycline;
 9-(D-phenylalanylamino)-7-chloro-6-demethylanhydrotetracycline;
 15 9-(D-glutamylamino)-7-chloro-6-demethylanhydrotetracycline;
 9-[(glycylacetyl)amino]-6-demethylanhydrotetracycline;
 9-[(L-alanylacetyl)amino]-6-demethylanhydrotetracycline;
 9-[(L-valylacetyl)amino]-6-demethylanhydrotetracycline;
 9-[(L-phenylalanylacetyl)amino]-6-demethylanhydrotetracycline;
 20 9-[(L-glutamylacetyl)amino]-6-demethylanhydrotetracycline;
 9-[(D-alanylacetyl)amino]-6-demethylanhydrotetracycline;
 9-[(D-valylacetyl)amino]-6-demethylanhydrotetracycline;
 9-[(D-phenylalanylacetyl)amino]-6-demethylanhydrotetracycline;
 9-[(D-glutamylacetyl)amino]-6-demethylanhydrotetracycline;
 25 9-(L-alanylamino)-6-demethylanhydrotetracycline
 9-(L-valylamino)-6-demethylanhydrotetracycline;
 9-(L-phenylalanylamino)-6-demethylanhydrotetracycline;
 9-(L-glutamylamino)-6-demethylanhydrotetracycline;
 9-(D-alanylamino)-6-demethylanhydrotetracycline
 30 9-(D-valylamino)-6-demethylanhydrotetracycline;
 9-(D-phenylalanylamino)-6-demethylanhydrotetracycline; and
 9-(D-glutamylamino)-6-demethylanhydrotetracycline.

The present invention also relates to useful intermediates of the formula

-20-

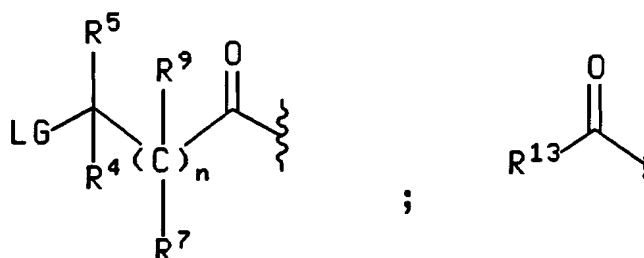
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III

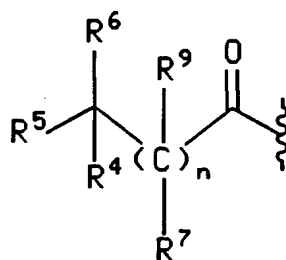
10 wherein R^{10} is a group of the formula

15



or

20



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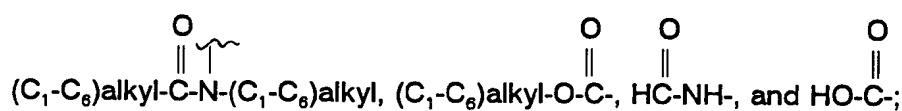
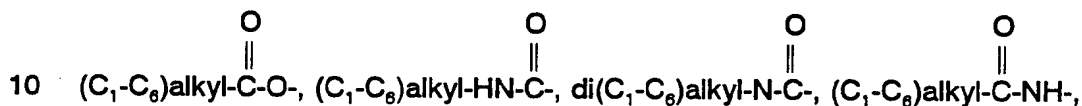
LG is chloro, bromo, iodo, $-\text{OSO}_2\text{Ph}$, $-\text{OSO}_2\text{PhCH}_3$, $-\text{OSO}_2\text{CH}_3$, or $-\text{OSO}_2\text{CF}_3$;

and wherein X, n, R^4 , R^5 , R^6 , R^7 , R^9 , R^{11} , R^{12} and R^{13} are as defined above for formula I.

30 Preferred compounds of the formula III are those wherein X is hydrogen and R^8 is $-\text{CONH}_2$.

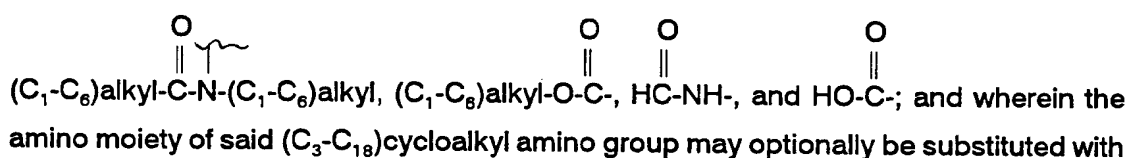
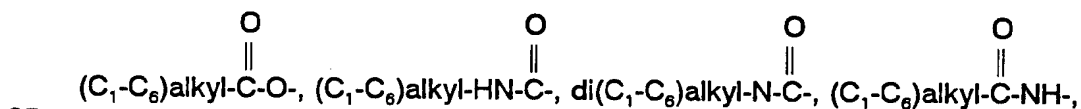
More preferred compounds of the formula III are those wherein n is zero; R^4 is hydrogen; and R^5 is hydrogen.

Most preferred compounds of the formula III are those wherein R⁶ is halogen, amino, hydroxylamino, (C₁-C₁₂)alkylamino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



15 (C₃-C₁₈)cycloalkylamino wherein the (C₃-C₁₈)cycloalkyl moiety of said (C₃-C₁₈)cycloalkyl amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano,

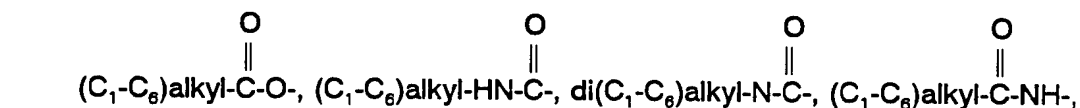
20 (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido, (C₁-C₆)alkyl,



30 (C₁-C₆)alkyl;

di(C₁-C₆)alkyl-amino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-

35 C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



-22-

$$\begin{array}{ccccccc} & \text{O} & & & \text{O} & \text{O} & \text{O} \\ & || & & & || & || & || \\ (C_1-C_6)\text{alkyl}-C-N-(C_1-C_6)\text{alkyl}, & (C_1-C_6)\text{alkyl}-O-C-, & HC-NH-, & \text{and} & HO-C-; \end{array}$$

(C_2-C_{10}) azacycloalkyl optionally substituted with one or more substituents,
 5 preferably one to three substituents, independently selected from halogen, hydroxy, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkylsulfonyl, trihalo (C_1-C_6) alkyl, amino, cyano,
 (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, amido, carboxamido,

10

$$\begin{array}{ccccccc} & \text{O} & & & \text{O} & & \text{O} \\ & || & & & || & & || \\ (C_1-C_6)\text{alkyl}-C-O-, & (C_1-C_6)\text{alkyl}-HN-C-, & di(C_1-C_6)\text{alkyl}-N-C-, & (C_1-C_6)\text{alkyl}-C-NH-, \end{array}$$

15

$$\begin{array}{ccccccc} & \text{O} & & & \text{O} & \text{O} & \text{O} \\ & || & & & || & || & || \\ (C_1-C_6)\text{alkyl}-C-N-(C_1-C_6)\text{alkyl}, & (C_1-C_6)\text{alkyl}-O-C-, & HC-NH-, & \text{and} & HO-C-; \end{array}$$

20

or R^5 and R^6 taken together may form a $-(CH_2)_pW(CH_2)_q-$ ring wherein W is

$$\begin{array}{ccc} \text{~} & \text{~} & \text{~} \\ | & | & | \\ \text{selected from } -N(C_1-C_3)\text{alkyl}, -CH_2-, -NH, O, S, \text{ and } -NOB; \end{array}$$
 wherein B is selected from hydrogen and (C_1-C_3) alkyl, p is an integer from one to three, and q is an integer from one to three.

25

The present invention also relates to a method for the prevention, treatment or control of bacterial infections in warm-blooded animals which comprises administering to said animal a pharmacologically effective amount of a compound of formula I, as defined above.

30 The present invention also relates to a pharmaceutical composition for the prevention, treatment or control of bacterial infections in warm-blooded animals which comprises a pharmacologically effective amount of a compound of formula I, as defined above, in association with a pharmaceutically acceptable carrier.

35 The present invention also relates to a method for the prevention, treatment or control of bacterial infections in warm-blooded animals which comprises administering to said animal a pharmacologically effective amount of a compound of formula II, as defined above.

The present invention also relates to a pharmaceutical composition for the prevention, treatment or control of bacterial infections in warm-blooded animals which

comprises a pharmacologically effective amount of a compound of formula II, as defined above, in association with a pharmaceutically acceptable carrier.

The present invention also relates to a method for treating or preventing osteoarthritis in mammals which comprises administering to said mammal a
5 pharmacologically effective amount of a compound of formula I, as described above.

The present invention also relates to a pharmaceutical compositions for treating or preventing osteoarthritis in mammals which comprises a pharmacologically effective amount of a compound of formula I, as defined above, in association with a pharmaceutically acceptable carrier.

10 (C₁-C₈)Alkyl, when used herein, refers to straight or branched alkyl groups such as methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methyl-propyl, 2-methylpropyl or 1,1-dimethylethyl.

(C₃-C₆)Cycloalkyl, when used herein, refers to saturated carbocyclic groups such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

15 Di(C₁-C₈)alkyl-amino, when used herein, refers to straight or branched alkyl amino groups such as ethyl(1-methylethyl)amino, diisopropyl amino, and methyl propyl amino.

(C₆-C₁₀)Aryl, when used herein, refers to such groups as phenyl, naphthyl or β-naphthyl.

20 (C₇-C₉)Aryl-(CH₂)_n-, when used herein, refers to such groups as benzyl, 1-phenylethyl, 2-phenylethyl or phenylpropyl.

(C₂-C₈)Azacycloalkyl, when used herein, refers to saturated nitrogen containing carbocycles such as pyrrolidine, piperidine, azetidine, homopiperidine, heptamethylenimine, piperazine, and N-methylpiperazine.

25 (C₁-C₈)alkylamino, refers to straight or branched alkyl groups which terminate in an amino group. Included in this group are such groups as aminomethyl, aminoethyl, aminopropyl or aminobutyl.

Carboxy-(C₁-C₈)alkylamino, refers to amino acids in which the point of attachment is the amine moiety and the acid can be separated from the amine by a
30 variable length alkyl chain. Included in this group are such groups as aminoacetic acid, aminobutyric acid, aminopropionic acid, β-amino propionic acid, or β-amino butyric acid.

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Hydroxy(C₁-C₈)alkyl, when used herein, refers to such groups as hydroxymethyl, hydroxyethyl, hydroxy-1-methylethyl or hydroxypropyl.

(C₁-C₈)Alkoxyamino, when used herein, refers to such groups as methoxyamino, ethoxyamino, n-propoxyamino, 1-methylethoxyamino, n-butoxyamino, 2-methylpropoxyamino, and 1,1-dimethylethoxyamino.

(C₃-C₈)Cycloalkyloxy, when used herein, refers to saturated carbocyclic groups covalently bonded to an oxygen heteroatom. The oxygen heteroatom forms the point of attachment. Included in this group are such groups as cyclopropoxy, trans-1,2-dimethylcyclopropoxy, cis-1,2-dimethylcyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, cycloheptoxy, cyclooctoxy, bicyclo[2.2.1]hept-2-yloxy, and bicyclo[2.2.2]oct-2-yloxy and the diastereomers and enantiomers of said (C₃-C₈)cycloalkoxy group.

(C₃-C₁₈)Cycloalkylamino, when used herein, refers to saturated carbocyclic groups covalently bonded to a nitrogen heteroatom. The nitrogen heteroatom forms the point of attachment. Included in this group are such groups as cyclopropylamino, cyclobutylamino, cyclohexylamino, cyclodecylamino, adamantylamino, bicyclobutylamino, bicyclodecylamino, and bicyclooctadecylamino.

Heterocycle-(CH₂)_k-, when used herein, refers to various heterocycles which are linked to the parent nucleus via an alkyl chain. One of ordinary skill in the art will understand that the phrase "wherein the heterocycle moiety of said heterocycle-(CH₂)_k-group may be, where possible, substituted with from one to three substituents" refers to the condition that any one of the substituents may form a covalent bond with each nitrogen or sulfur heteroatom or a carbon atom when that heteroatom or carbon atom possesses less than the maximum number of bonds possible. One of ordinary skill in the art will also understand that the heterocycle moiety may be connected to the alkyl chain via one of the ring heteroatoms or carbon atoms.

(C₆-C₁₀)Aryl-(CH₂)_i-oxyamino, when used herein, refers to such groups as phenoxyamino, naphthyloxyamino or β-naphthyloxy amino.

O
||

The group (C₁-C₈)alkyl-O-C-amino, when used herein, refers to such groups as methoxycarbonylamino, ethoxycarbonylamino, allyloxycarbonylamino, propoxycarbonylamino, isopropoxycarbonylamino, 1,1-dimethylethoxycarbonylamino, n-butoxycarbonylamino, and 2-methylpropoxycarbonylamino.

-25-

Halogen, when used herein, refers to fluorine, chlorine, bromine or iodine.

The term "warm-blooded animals" when used herein refers to such animals as mammals, fish and birds. "Tetracycline sensitive microorganisms" when used herein refers to those microorganisms that are still susceptible to known tetracycline
5 compounds such as oxytetracycline, chlorotetracycline, tetracycline, 7-chloro-6-demethyltetracycline, 6-demethyltetracycline, doxycycline, methacycline, and minocycline.

"Tetracycline resistant microorganisms" when used herein refers to those microorganisms that are no longer susceptible to most of the known tetracycline
10 compounds listed above. Two major mechanisms of bacterial resistance to these tetracyclines are: a) energy-dependent efflux of the antibiotic mediated by proteins located in the cytoplasmic membrane which prevents intracellular accumulation of tetracyclines (S. B. Levy, et al., Antimicrob. Agents Chemotherapy 33, 1373-1374 (1989); and b) ribosomal protection mediated by a cytoplasmic protein which interacts
15 with the ribosome such that tetracycline no longer binds or inhibits protein synthesis (A. A. Salyers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol., 4:151-156, 1990). The efflux mechanism of resistance is encoded by resistance determinants designated tetA-tetL. They are common in many Gram-negative bacteria (resistance genes Class A-E), such as Enterobacteriaceae, Pseudomonas, Haemophilus and Aeromonas, and
20 in Gram-positive bacteria (resistance genes Class K and L), such as Staphylococcus, Bacillus and Streptococcus. The ribosomal protection mechanism of resistance is encoded by resistance determinants designated TetM, N and O, and is common in Staphylococcus, Streptococcus, Campylobacter, Gardnerella, Haemophilus and Mycoplasma (A. A. Salyers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol., 4:151-
25 156 1990).

A particularly useful tetracycline compound is 7-(dimethylamino)-6-demethyl-6-deoxytetracycline, known as minocycline (see U.S. 3,148,212, RE 26,253 and 3,226,436). However, strains harboring the tetB (efflux in gram-negative bacteria) mechanism, but not tetK (efflux in Staphylococcus) are resistant to minocycline. Also,
30 strains carrying tetM (ribosomal protection) are resistant to minocycline. The compounds of the present invention demonstrate significant in vitro and in vivo activity in tetracycline and minocycline susceptible strains and some tetracycline and

minocycline resistant strains, that is, those harboring the tetM (ribosomal protection) resistance determinants.

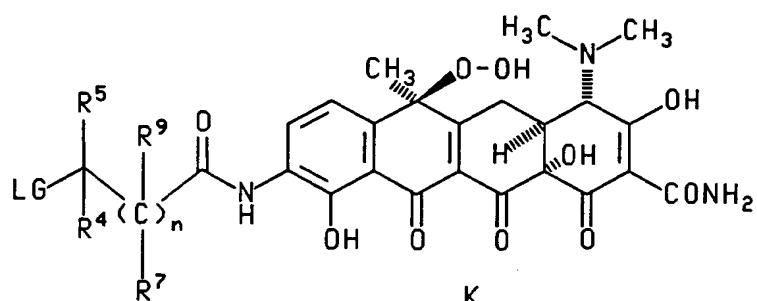
Detailed Description of the Invention

In the reaction Schemes and description which follow h, j, k, m, n, p, q, r, s, X,
5 R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², and R¹³ as well as structural formulae I, II
and III are as defined above.

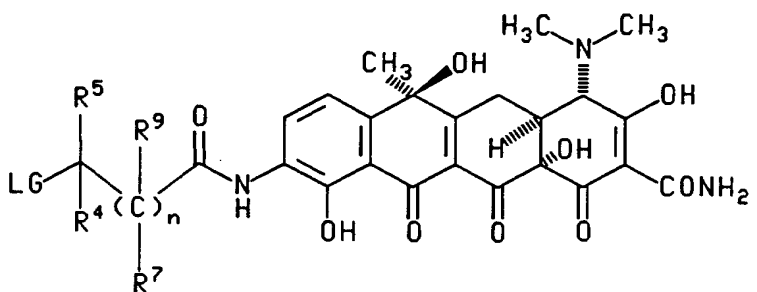
-27-

Scheme 1

B



K



L



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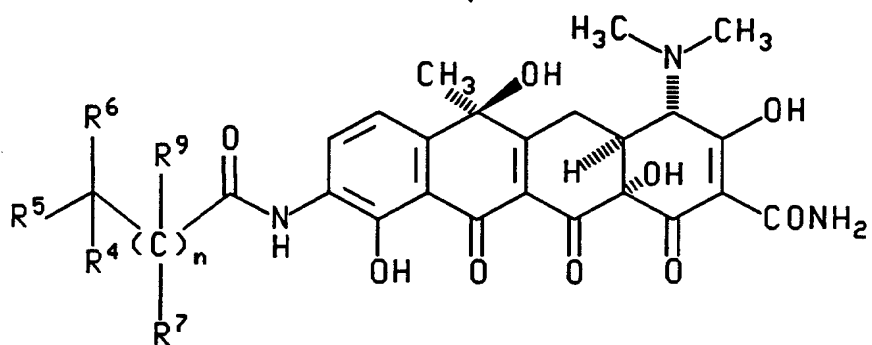
Scheme 1 cont'd

L

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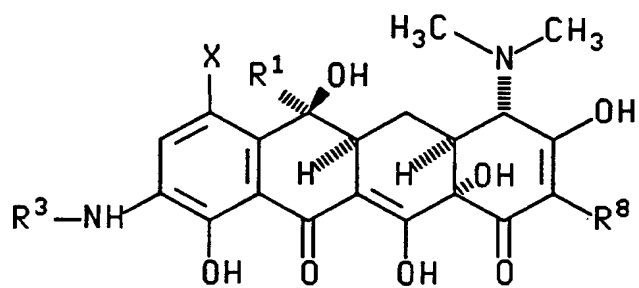
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M



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I

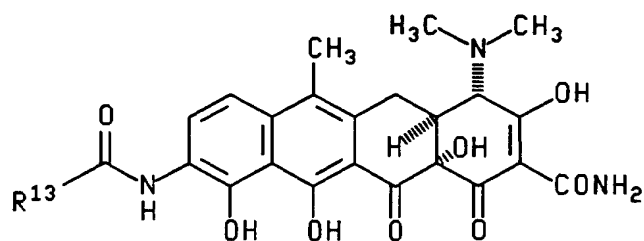
-29-

Scheme 2

5



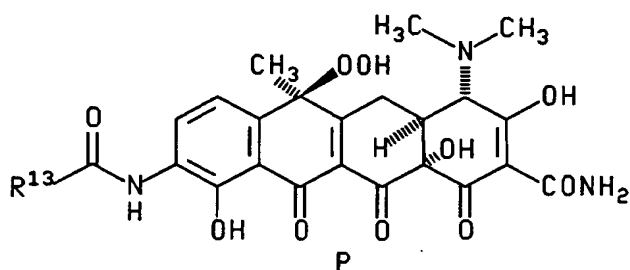
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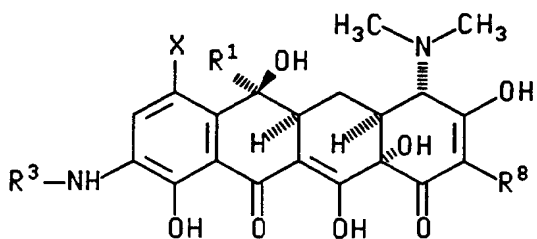
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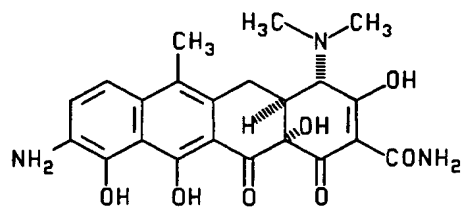


I

-30-

Scheme 3

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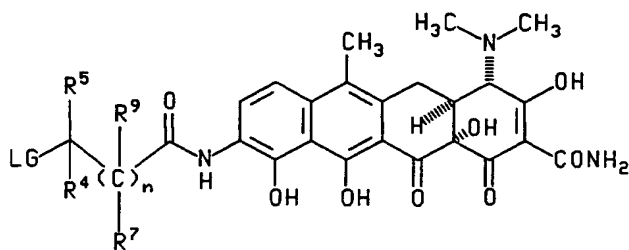


A

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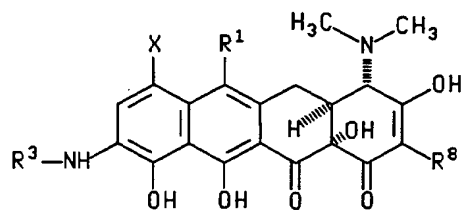


B

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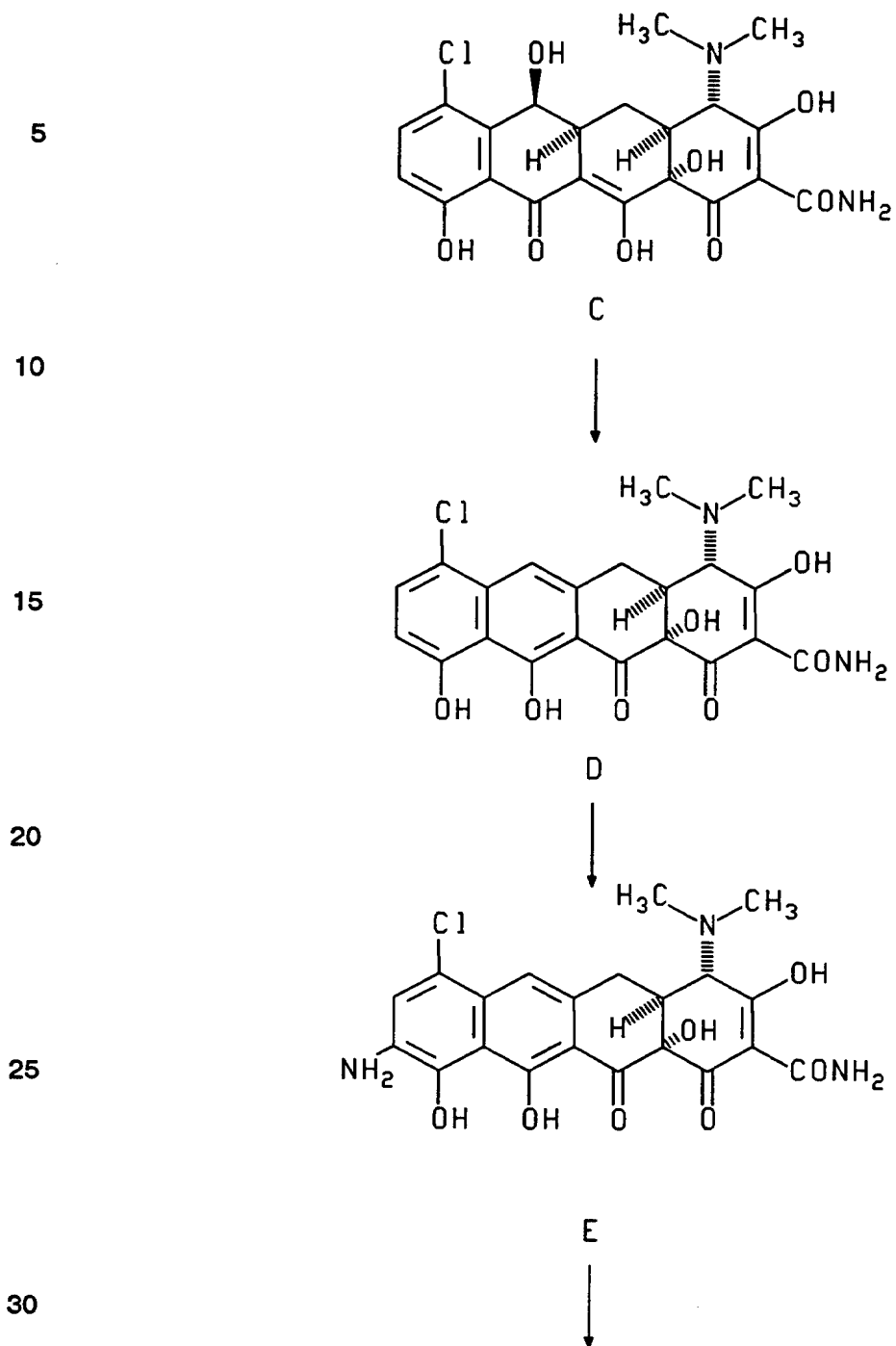


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II

-31-

Scheme 4



-32-

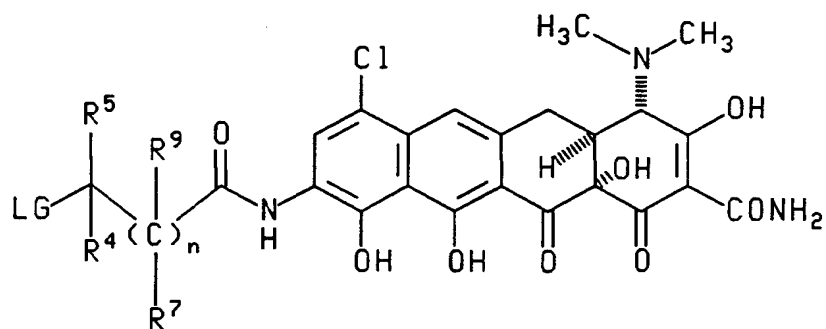
Scheme 4 cont'd

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E



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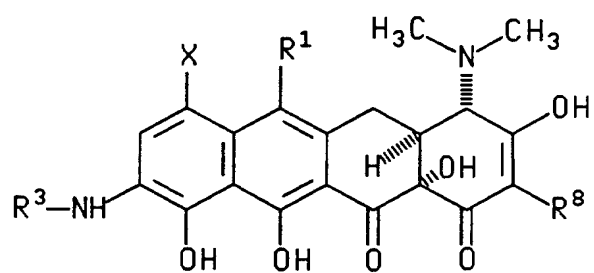


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F



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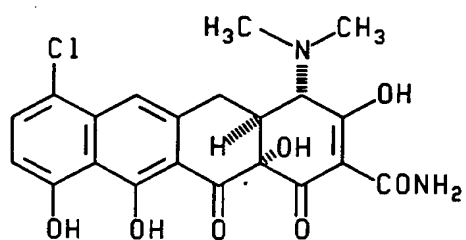
II

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-33-

Scheme 5

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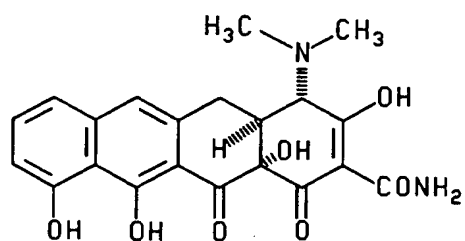


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D



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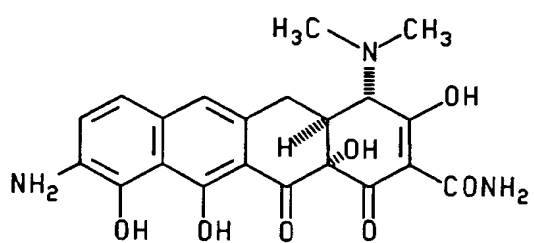


20

G



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H



-34-

Scheme 5 cont'd

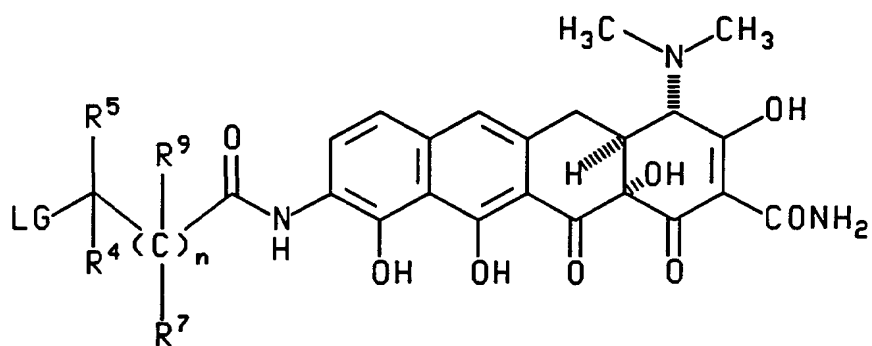
H



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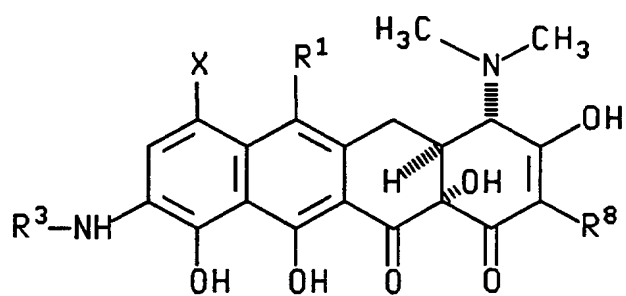


J



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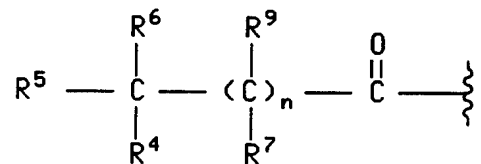
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30

II

Scheme 1 refers to the preparation of compounds of the formula I wherein R³ is a group of the formula



X is hydrogen, and R¹ is methyl.

Referring to Scheme 1, the compounds of formula I can be prepared from a compound of formula M by reduction in a reaction inert solvent. This reduction can be mediated either by transition metals or other metal reducing agents. When a transition metal mediates the reduction, a hydrogen source is also used. Suitable transition metals include palladium on carbon, palladium hydroxide on carbon, platinum oxide and platinum on activated carbon. Platinum oxide is preferred. Suitable hydrogen sources include hydrogen gas, ammonium formate and formic acid. Hydrogen gas at a pressure of about one to about three atmospheres (approximately 50 psi) is the preferred hydrogen source. Three atmospheres of hydrogen gas is the preferred pressure. Suitable solvents include (C₁ to C₄) alcohols, acetonitrile, N,N-dimethylformamide, N-methylpyrrolidinone and dilute aqueous acids such as hydrochloric or sulfuric acid. Methanol is the preferred solvent. The reaction time is one to four hours, preferably two hours. Other metal reducing agents include iron sulfate (FeSO₄), zinc (Zn) (metal) in glacial acetic acid, magnesium (Mg) in methanol and Zn (metal) in aqueous hydrochloric acid. Suitable solvents include excess of the solvent used to suspend the metal reducing agent, such as glacial acetic acid, methanol and aqueous hydrochloric acid. All of the above reduction reactions are usually conducted at a temperature from about 25°C to about 100°C, preferably about 25°C.

The compound of the formula M can be formed by reaction of a compound of the formula L with an amine reagent, wherein the amine reagent is an amine group as described above as the substituent R⁶. Suitable solvents include (C₁ to C₄) alcohols, dimethyl sulfoxide, N,N-dimethylformamide, N-methylpyrrolidinone, acetonitrile, water, and acetone and mixtures of these solvents. Acetonitrile/ N-methylpyrrolidinone (1:1)

-36-

or water mixtures are the preferred solvents. Optionally, the reaction may be run in the presence of a base, preferably 4 to 20 equivalents of the amine reagent, most preferably 4 equivalents of the amine reagent. A base other than the amine reagent may be used in the reaction, suitable bases include sodium hydroxide, potassium
5 hydroxide, triethylamine, sodium carbonate, cesium carbonate, and sodium hydrogen carbonate. The amine reagent is the preferred base. The reaction is usually conducted at a temperature of about 20°C to about 50°C, preferably at about 25°C. The reaction time is about 5 minutes to about 30 minutes, preferably 15 minutes.

The compound of formula L may be prepared by reduction of a peroxide of the
10 formula K. This reduction can be mediated either by transition metals or other metal reducing agents. When a transition metal mediates the reduction, a hydrogen source is also used. Suitable transition metals include palladium on carbon, palladium hydroxide on carbon, rhodium on carbon, platinum on activated carbon and platinum oxide. Five percent rhodium on carbon is preferred. Suitable hydrogen sources
15 include hydrogen gas, ammonium formate and formic acid. Hydrogen gas at a pressure of about one to about three atmospheres is the preferred hydrogen source. Three atmospheres of hydrogen gas (approximately 50 psi) is the preferred pressure. Suitable solvents include (C₁ to C₄) alcohols, acetonitrile, N,N-dimethylformamide and N-methylpyrrolidinone. Methanol is the preferred solvent. The reaction time is about
20 5 to about 15 minutes, preferably about 5 minutes. Other peroxide reducing agents include sodium dithionite (Na₂S₂O₄), and sodium bisulfite. Suitable solvents for these other peroxide reducing reactions include water, lower alcohols such as methanol and ethanol, water and mixtures thereof. All of the above reduction reactions are usually conducted at a temperature of from about 25°C to about 100°C, preferably about
25 25°C to about 50°C. It should be noted that compounds of formula L often can be used directly from the reduction reaction without chromatographic purification.

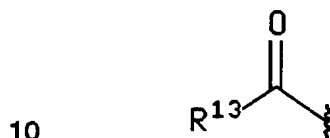
The peroxides of formula K may be prepared by reaction of a compound of the formula B with singlet oxygen in a reaction inert solvent. The reaction is facilitated by a sensitizer such as Rose Bengal, methylene blue, or 5, 10, 15, 20-tetraphenyl-21 H,
30 23 H-porphine (TPP), preferably 5, 10, 15, 20-tetraphenyl-21H, 23H-porphine. Singlet oxygen is produced by passing oxygen gas through the reaction mixture while the reaction mixture is irradiated with visible light with an intensity from about 300 Watts to about 600 Watts, preferably about 450 Watts. Suitable solvents for the aforesaid

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process include (C₁-C₄) alcohols, methylene chloride, and chloroform, and mixtures thereof. Preferably the solvent is a mixture of chloroform/methanol (25:1). The reaction is usually conducted at a temperature from about 0°C to about 50°C, preferably at about 25°C. The reaction time is usually about 10 minutes to about 1 hour, preferably about 15 minutes.

Compounds of the formula B which is the starting material for the processes of Scheme 1 can be prepared by the methods of Scheme 3.

Scheme 2 refers to the preparation of compounds of the formula I wherein R³ is a group of the formula



wherein X is hydrogen, and R¹ is methyl.

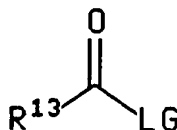
Referring to Scheme 2, the compounds of formula I can be prepared from a compound of formula P by reduction in a reaction inert solvent. This reduction can be mediated either by transition metals or other metal reducing agents. When a transition metal mediates the reduction, a hydrogen source is also used. Suitable transition metals include palladium on carbon, palladium hydroxide on carbon, rhodium on carbon, and platinum on activated carbon and platinum oxide. Platinum oxide is the preferred transition metal. Suitable hydrogen sources include hydrogen gas, ammonium formate and formic acid. Hydrogen gas at a pressure of about one to about three atmospheres is the preferred hydrogen source. Three atmospheres of hydrogen gas (approximately 50 psi) is the preferred pressure. Suitable solvents include (C₁ to C₄) alcohols, acetonitrile, N,N-dimethylformamide and N-methylpyrrolidone. Methanol is the preferred solvent. The reaction time is about 1 to about 5 hours, preferably about 2 hours. Other metal reducing agents include zinc (Zn) (metal) in glacial acetic acid, magnesium (Mg) in methanol and Zn (metal) in aqueous hydrochloric acid. Zinc metal is the preferred reducing agent of this group. Suitable solvents include excess of the solvent used to suspend the metal reducing agent, such as glacial acetic acid, methanol and aqueous hydrochloric acid. All of the above

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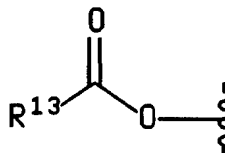
reduction reactions are usually conducted at a temperature of from about 25°C to about 100°C, preferably about 25°C to about 50°C.

The compounds of the formula P may be prepared by reaction of a compound of the formula O with singlet oxygen in a reaction inert solvent according to the methods described in Scheme 1 for the preparation of compounds of the formula K.

The compounds of the formula O can be prepared from a compound of the formula A by reaction with a group of the formula



wherein LG is a leaving group such as chloro, bromo, iodo, -OSO₂Ph, -OSO₂PhCH₃, -OSO₂CH₃, or -OSO₂CF₃ in an inert solvent in the presence of base. Alternatively, LG can form a mixed anhydride group of the formula



such as acetic anhydride. The preferred leaving group is chloro. Suitable solvents include dimethyl sulfoxide, N,N-dimethylformamide, N-methylpyrrolidinone, acetonitrile, and acetone. N-methylpyrrolidinone is the preferred solvent. Suitable bases include sodium hydroxide, potassium hydroxide, triethylamine, sodium carbonate, cesium carbonate, and sodium hydrogen carbonate. Sodium hydrogen carbonate is the preferred base. The reaction is usually conducted at a temperature of about 20°C to about 50°C, preferably at about 25°C.

Compounds of the formula A which is the starting material for the processes of Scheme 2 can be prepared by the methods detailed in M. Menachery and M. Cava., "Amino Derivatives of Anhydrotetracyclines", Can. J. Chem., **62**, 2583-2584 (1984).

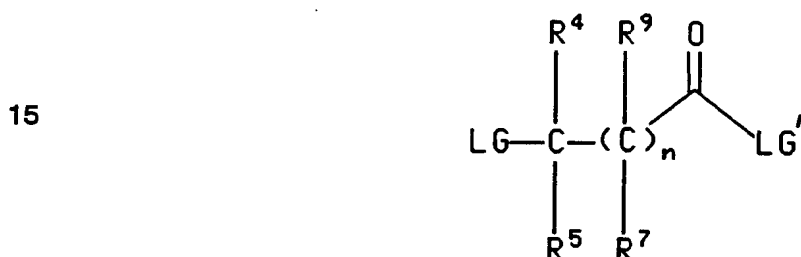
Scheme 3 refers to the preparation of compounds of the formula II wherein X is hydrogen and R¹ is methyl.

Referring to Scheme 3, the compound of the formula II can be formed by reaction of a compound of the formula B with an amine reagent, wherein the amine reagent is an amine group as described above as the substituent R⁸. Suitable solvents

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include (C₁ to C₄) alcohols, dimethyl sulfoxide, N,N-dimethylformamide, N-methylpyrrolidinone, acetonitrile, water, and acetone and mixtures of these solvents. Acetonitrile/ N-methylpyrrolidinone (1:1) or water mixtures are the preferred solvents. Optionally, the reaction may be run in the presence of a base, preferably 4 to 20
 5 equivalents of the amine reagent, most preferably 4 equivalents of the amine reagent. A base other than the amine reagent may be used in the reaction, suitable bases include sodium hydroxide, potassium hydroxide, triethylamine, sodium carbonate, cesium carbonate, and sodium hydrogen carbonate. The amine reagent is the preferred base. The reaction is usually conducted at a temperature of about 20°C to
 10 about 50°C, preferably at about 25°C.

Compounds of the formula B can be prepared from a compound of formula A by reaction with a compound of formula



, wherein LG and LG' are each independently selected from a leaving group such as
 20 chloro, bromo, iodo, -OSO₂Ph, -OSO₂PhCH₃, -OSO₂CH₃, or -OSO₂CF₃, in an inert solvent in the presence of base. The preferred leaving group for both LG and LG' is bromo. Suitable solvents include dimethyl sulfoxide, N,N-dimethylformamide, N-methylpyrrolidinone, acetonitrile, and acetone. N-methylpyrrolidinone is the preferred solvent. Suitable bases include sodium hydroxide, potassium hydroxide, triethylamine,
 25 sodium carbonate, cesium carbonate, and sodium hydrogen carbonate. Sodium hydrogen carbonate is the preferred base. The reaction is usually conducted at a temperature of about 10°C to about 100°C, preferably at about 25°C.

Compounds of the formula II wherein R³ is a group of the formula



are compounds of the formula O in Scheme 2.

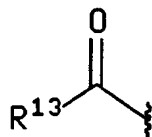
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The compound of the formula A which is the starting material for the processes of Scheme 2 can be prepared by the methods detailed in M. Menachery and M. Cava., "Amino Derivatives of Anhydrotetracyclines", Can. J. Chem., 62, 2583-2584 (1984).

Scheme 4 refers to the preparation of compounds of the formula II wherein X is chloro and R¹ is hydrogen.

Referring to Scheme 4, the compound of the formula II can be prepared by reaction of a compound of the formula F with an amine reagent, wherein the amine reagent is an amine group as described above as the substituent R⁶. Suitable solvents include (C₁ to C₄) alcohols, dimethyl sulfoxide, N,N-dimethylformamide, N-methylpyrrolidinone, acetonitrile, water, and acetone and mixtures of these solvents. Acetonitrile/ N-methylpyrrolidinone (1:1) or water mixtures are the preferred solvents. Optionally, the reaction may be run in the presence of a base, preferably 4 to 20 equivalents of the amine reagent, most preferably 4 equivalents of the amine reagent. A base other than the amine reagent may be used in the reaction, suitable bases include sodium hydroxide, potassium hydroxide, triethylamine, sodium carbonate, cesium carbonate, and sodium hydrogen carbonate. The amine reagent is the preferred base. The reaction is usually conducted at a temperature of about 20°C to about 50°C, preferably at about 25°C.

Alternatively, compounds of the formula II wherein R³ is a group of the formula

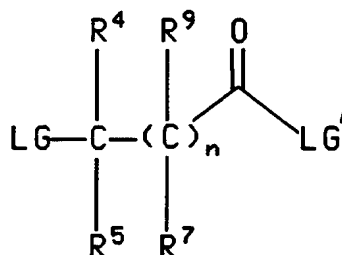


and X is chloro and R¹ is hydrogen, can be prepared from compounds of the formula E according to the methods described above in Scheme 2 for the preparation of compounds of the formula O from compounds of the formula A.

Compounds of the formula F can be prepared from a compound of formula E by reaction with a compound of formula

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, wherein LG and LG' are each independently selected from a S_N2 leaving group such as chloro, bromo, iodo, -OSO₂Ph, -OSO₂PhCH₃, -OSO₂CH₃, or -OSO₂CF₃, in an inert solvent in the presence of base. The preferred leaving group is bromo. Suitable solvents include dimethyl sulfoxide, N,N-dimethylformamide, N-methylpyrrolidinone, acetonitrile, and acetone. N-methylpyrrolidinone is the preferred solvent. Suitable bases include sodium hydroxide, potassium hydroxide, triethylamine, sodium carbonate, cesium carbonate, and sodium hydrogen carbonate. Sodium hydrogen carbonate is the preferred base. The reaction is usually conducted at a temperature of about 10°C to about 100°C, preferably at about 25°C.

An amine compound of the formula E can be prepared in two steps from a compound of the formula D. In the first step, the compound of the formula D is transformed into a nitroso intermediate by nitrosation with nitrous acid in an inert solvent. Suitable solvents include aqueous acid solution, such as aqueous hydrochloric, acetic acid, or aqueous sulfuric acid. Nitrous acid is prepared in situ according to methods well known to those of ordinary skill in the art. Preferably, sodium nitrite is dissolved in an aqueous acid solution, such as aqueous hydrochloric, acetic acid, or aqueous sulfuric acid. Aqueous hydrochloric acid is the preferable solvent. The temperature of the reaction may be in the range from about 0°C to about 50°C, preferably about 10°C.

The nitroso intermediate is then reduced to the amine of formula E by reaction with a reducing agent in a reaction inert solvent. Suitable reducing agents include sodium dithionite in aqueous base, iron in glacial acetic acid, and zinc in acetic acid. One to about ten equivalents of the reducing agent can be used in the reaction. Preferably, 5 equivalents of the reducing agent is used. The preferred reducing agent is sodium dithionite. When sodium dithionite is the reducing agent, a base must be employed. Suitable bases include sodium hydroxide, potassium hydroxide and ammonium hydroxide. Preferably, the base is sodium hydroxide. The pH of the

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reduction when sodium dithionite is employed as the reducing agent is in the range of about 8 to about 12, preferably about 9. The reaction time is about 15 minutes to about 45 minutes, preferably about 30 minutes.

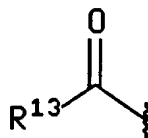
The compound of the formula D can be prepared from 7-chloro-6-demethyltetracycline by treatment with a strong aqueous acid. Suitable acids include concentrated sulfuric, hydrochloric or phosphoric acids. The preferred acid is concentrated hydrochloric acid. This reaction is usually conducted at a temperature of from about 25°C to about 100°C, preferably about 50°C to about 70°C. The reaction time for the aforesaid reaction is in the range from about 30 minutes to about 2 hours, preferably about one hour. It should be noted that compounds of formula D often can be used directly from the reduction reaction without chromatographic purification.

7-Chloro-6-demethyltetracycline, the compound of formula C, is commercially available.

Scheme 5 refers to the preparation of compounds of the formula II wherein X is hydrogen and R¹ is hydrogen.

Referring to Scheme 5, compounds of the formula II can be formed by reaction of a compound of the formula J with an amine reagent according to the methods described in Scheme 3 for the preparation of compounds of the formula II from compounds of the formula B.

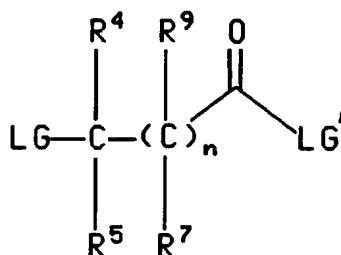
Alternatively, compounds of the formula II wherein R³ is a group of the formula



can be prepared from compounds of the formula H according to the methods of Scheme 2 for the preparation of compounds of the formula O from compounds of the formula A.

Compounds of the formula J can be prepared from a compound of formula H by reaction with a compound of formula

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, wherein LG and LG' are each independently selected from n S_n2 leaving group such as chloro, bromo, iodo, -OSO₂Ph, -OSO₂PhCH₃, -OSO₂CH₃, or -OSO₂CF₃, in an inert solvent in the presence of base. The preferred leaving group is bromo. Suitable solvents include dimethyl sulfoxide, N,N-dimethylformamide, N-methylpyrrolidinone, acetonitrile, and acetone. N-methylpyrrolidinone is the preferred solvent. Suitable bases include sodium hydroxide, potassium hydroxide, triethylamine, sodium carbonate, cesium carbonate, and sodium hydrogen carbonate. Sodium hydrogen carbonate is the preferred base. The reaction is usually conducted at a temperature of about 10°C to about 100°C, preferably at about 25°C.

The compound of the formula H can be prepared from the compound of the formula G by reaction with nitrous acid in an inert solvent according to the methods used in Scheme 4 for the preparation of the compound of the formula E from the compound of formula D.

The compound of the formula G can be prepared from the compound of the formula D by reduction in a reaction inert solvent. This reduction is mediated by transition metals in the presence of a hydrogen source. Suitable transition metals include palladium on carbon, rhodium on carbon, palladium hydroxide on carbon and platinum oxide. Ten percent palladium on carbon is preferred. Suitable hydrogen sources include hydrogen gas, ammonium formate and formic acid. Hydrogen gas at a pressure of about one to about three atmospheres is the preferred hydrogen source. Three atmospheres of hydrogen gas is the preferred pressure. Suitable solvents include (C₁ to C₄) alcohols, acetonitrile, ethyl acetate, N,N-dimethylformamide and N-methylpyrrolidinone. Methanol is the preferred solvent. All of the above reduction reactions are usually conducted at a temperature of from about 25°C to about 100°C, preferably about 25°C. The reaction time is about 30 minutes to about 2 hours, preferably about one hour. It should be noted that the compound of formula G often can be used directly from the reduction reaction without chromatographic purification.

The compound of the formula D is prepared as described in Scheme 4.

Compounds of the formula I and II wherein R^8 is $-\text{CONHCH}_2-\text{NR}^{11}\text{R}^{12}$ are prepared from compounds of the formula I and II wherein R^8 is $-\text{CONH}_2$ by reaction with formaldehyde and a compound of the formula $\text{HNR}^{11}\text{R}^{12}$ in a reaction inert solvent.

- 5 Suitable solvents for the aforesaid process include (C_1 to C_4) alcohols, acetonitrile, ethyl acetate, N,N-dimethylformamide and N-methylpyrrolidinone. t-Butyl alcohol is the preferred solvent. The aforesaid reaction is usually conducted at a temperature of from about 25°C to about 100°C , preferably about 100°C .

- Unless indicated otherwise, the pressure of each of the above reactions is not
10 critical. Generally, the reactions will be conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one atmosphere).

- The compounds of the formula I or II which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals,
15 it is often desirable in practice to initially isolate a compound of the formula I or II from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared
20 by treating the free base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

- The acids which are used to prepare the pharmaceutically acceptable acid
25 addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, e.g., salts containing pharmacologically acceptable anions, such as chloride, bromide, iodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [e.g., 1,1'-methylene-
30 bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds of the formula I or II which are also acidic in nature, e.g., where R^3 contains a carboxylate, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal

or alkaline-earth metal salts and in particular, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I or II. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of the reaction with maximum yields of the desired final product.

The compounds of formulae I and II of the present invention are useful in the prevention, treatment or control of bacterial infections in mammals, fish and birds. The compounds of formulae I and II exhibit broad-spectrum activity against both Gram-positive and Gram-negative aerobic and anaerobic bacteria including organisms that are resistant to tetracycline. The antibacterial activity of the compounds of the present invention against bacterial pathogens is demonstrated by the compound's ability to inhibit growth of Pasteurella multocida, Pasteurella haemolytica and E. coli. The following procedures are typical assays. Assay I is utilized to test for activity against tetracycline resistant or sensitive Pasteurella multocida and E. coli and Assay II is utilized to test for activity against Pasteurella haemolytica.

Assay I (P. multocida and E. coli assay)

This assay is based on a liquid dilution method in microtiter format. A single colony of tetracycline (tet) resistant or sensitive P. multocida or E. coli is inoculated into 5 ml of brain heart infusion (BHI) broth supplemented with tetracycline as a selective pressure (15 μ g/ml and 100 μ g/ml, respectively). The test compounds are prepared by solubilizing 1 mg of the compound in 125 μ l of dimethylsulfoxide (DMSO). Dilutions of the test compound are prepared using uninoculated unsupplemented BHI broth with tetracycline. The concentrations of the test compound used range from 200 μ g/ml to

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0.098 $\mu\text{g/ml}$ by two-fold serial dilutions. The P. multocida or E. coli culture is diluted with uninoculated unsupplemented BHI broth with tetracycline. This diluted cell suspensions are mixed with respective serial dilutions of the test compound to make a $10^5/\text{ml}$ of final cell concentration and incubated at 37°C for 18 hours. The minimum
5 inhibitory concentration is equal to the concentration of the compound exhibiting 100% inhibition of growth of P. multocida or E. coli as determined by comparison with an uninoculated control.

All of the compounds of formula I and II which were tested had an MIC less than 100 $\mu\text{g/ml}$ against Pasteurella multocida and Pasteurella haemolytica. All of the
10 compounds of formula I which were tested had an MIC less than 100 $\mu\text{g/ml}$ against E. coli.

Assay II (P. haemolytica)

This assay is based on an agar dilution method using a manual multiple inoculator such as a Steers Replicator®. Two to five colonies isolated from an agar
15 plate are inoculated into BHI broth and incubated overnight at 37°C with shaking (200 rpm). The next morning, 300 μl of the fully grown P. haemolytica preculture is inoculated into 3 ml of fresh BHI broth and is incubated at 37°C with shaking (200 rpm). The appropriate amounts of the test compounds are dissolved in ethanol and a series of two-fold serial dilutions are prepared. Two ml of the respective serial dilution
20 is mixed with 18 ml of molten BHI agar and solidified. When the inoculated P. haemolytica culture reaches 0.5 McFarland standard density (a density comparison of an unknown inoculum preparation to a standard Barium sulfate suspension), about 5 μl of the P. haemolytica culture is inoculated onto BHI agar plates containing the various concentrations of the test compound using a Steers Replicator and incubated
25 for 18 hours at 37°C . Initial concentrations of the test compound range from 100-200 $\mu\text{g/ml}$. The MIC is equal to the concentration of the test compound exhibiting 100% inhibition of growth of P. haemolytica as determined by comparison with an uninoculated control.

The in vivo activity of the compounds of formula I or II can be determined by
30 conventional animal protection studies well known to those skilled in the art. Usually these studies are carried out in mice.

Mice are allotted to cages (10 per cage) upon their arrival, and allowed to acclimate for a minimum of 48 hours before being used. Animals are inoculated with

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0.5 ml of a 3×10^3 colony forming unit (CFU)/ml bacterial suspension (*P. multocida*) intraperitoneally. Each experiment has at least 3 non-medicated control groups including one infected with 0.1X challenge dose and two infected with 1X challenge dose; a 10X challenge data group may also be used. Generally, all mice in a given study can be challenged within 30-90 minutes, especially if a repeating syringe (such as a Cornwall® syringe) is used to administer the challenge. Thirty minutes after challenging has begun, the first compound treatment is given. It may be necessary for a second person to begin compound dosing if all of the animals have not been challenged at the end of 30 minutes. The routes of administration are subcutaneous or oral. Subcutaneous doses are administered into the loose skin in the back of the neck whereas oral doses are given by means of a feeding needle. In both cases, a volume of 0.2 ml is used per mouse. Compounds are administered 30 minutes, 4 hours, and 24 hours after challenge. A control compound of known efficacy administered by the same route is included in each test. Animals are observed daily, and the number of survivors in each group is recorded. The *P. multocida* model monitoring continues for 96 hours (four days) post challenge. Surviving mice are asphyxiated with carbon dioxide at the end of the study.

The PD_{50} is a calculated dose at which the compound tested protects 50% of a group of mice from mortality due to the bacterial infection which would be lethal in the absence of drug treatment.

To implement the methods of this invention for the treatment, prevention, or control of bacterial infections, an effective dose of a compound of formula I or II is administered to a susceptible or infected animal by parenteral (i.v., i.m. or s.c.), oral or topical route. The effective dose will vary with the severity of the disease, and the age, weight and condition of the animal. However, the dose will usually range from about 0.1 to about 150 mg/kg of body weight per day, preferably from about 0.1 to about 50 mg/kg.

The *in vivo* activity of the compounds of the invention for the treatment or prevention of osteoarthritis may be determined according to the methods of Yu *et al.* in *Arthritis and Rheumatism*, 34 (10), 1150-1159 (1992).

To implement the methods of this invention for the treatment or prevention of osteoarthritis, an effective dose of a compound of formula I or II is administered to a mammal by parenteral (i.v., i.m. or s.c.), oral, buccal or topical route. The effective

dose will vary with the nature and severity of the disease, and the age, weight and condition of the animal. However, the dose will usually range from about 0.1 to about 150 mg/kg of body weight per day, preferably from about 0.1 to about 50 mg/kg. The dosage regime may be adjusted to provide the optimal therapeutic response.

5 This invention also provides a method of treating, preventing or controlling a bacterial infection or a mycoplasmic infection in an animal in need of such treatment, prevention or control comprising administering to said animal a bacterial or mycoplasmic effective amount of a compound of the formula (I) or (II) or a pharmaceutically acceptable salt thereof.

10 This invention also provides a method of treating or preventing osteoarthritis in an animal in need of such treatment or prevention comprising administering to said animal a bacterial or mycoplasmic treating amount of a compound of the formula (I) or (II) or a pharmaceutically acceptable salt thereof.

 The compositions of the present invention may be formulated in a conventional
15 manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration by inhalation or insufflation.

 The active compounds may be formulated for parenteral administration by
20 injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative if needed. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing
25 agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle before use, e.g., sterile pyrogen-free water.

 A suitable vehicle for parenterally administering either the antibiotic or osteoarthritic dose is a solution of the compound in sterile water, or a solution of the compound in a solvent comprising at least 50% water and a pharmaceutically
30 acceptable cosolvent or cosolvents such as methanol, ethanol, isopropyl alcohol, propylene glycol, glycerol, carbonate esters like diethyl carbonate, dimethyl sulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidinone, and the like. Suspensions are also suitable vehicles for administering the compounds of this

invention. The suspending medium can be, for example, aqueous carboxymethyl cellulose, inert oils such as peanut oil, highly refined mineral oils, aqueous polyvinylpyrrolidone and so forth. Suitable physiologically acceptable adjuvants may be necessary to maintain the compound in suspension. These adjuvants may be
5 chosen from among thickeners such as carboxymethyl cellulose, polyvinylpyrrolidone, gelatin, and the alginates. Surfactants are also useful as suspending agents. These surfactants include: lethicin, alkylphenol polyethylene oxide adducts, naphthalenesulfonates, alkylbenzenesulfonates and polyoxyethylene sorbitan esters. Agents affecting surface tension can also help in making useful suspensions. Such
10 agents include silicone antifoams, sorbitol, and sugars. For intravenous use the total concentration of solutes should be controlled to render the preparation isotonic. Thus in a further aspect the invention provides pharmaceutical compositions comprising a compound of the formula (I) or (II) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

15 For oral administration, either of the osteoarthritis or antibiotic pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate);
20 lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable
25 vehicles before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

30 For buccal administration either of the antibiotic or osteoarthritis compositions may take the form of tablets or lozenges formulated in a conventional manner.

The active compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of an active compound and a suitable powder base such as lactose or starch.

Typical unit dosage forms for topical administration will contain about 0.5 wt. % to about 10 wt. %, preferably about 1 wt. % to about 3.5 wt. %, most preferably about 2.5 wt. % to about 3.5 wt. % of a compound of formula I or II, based on the entire weight of the composition per topical unit dose application. If the composition is intended for sustained release such as by using microcapsules or microspheres, much larger amounts of the active ingredient would of course be incorporated into an individual unit.

For topical administration, solutions or suspensions of a therapeutic agent in clear or milky lotions, gels, creams, ointments, sprays, lip balm, clothwipe, impregnated bandages and other topical and transdermal delivery devices may be employed.

Suitable solvents or vehicles, for instance, for the topical antibiotic or osteoarthritic composition of the present invention includes methanol, ethanol, propanol, acetone, n-butyl alcohol, isobutyl alcohol and the like.

The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuterio-dimethylsulfoxide (DMSO- d_6) unless otherwise specified). Commercial reagents were utilized without further purification. THF refers to tetrahydrofuran. DMF refers to dimethylformamide. Preparative High Pressure Liquid Chromatography (HPLC)

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was carried out using reverse-phase C-8 or C-18 silica gel using the appropriate mixture of water, acetonitrile and trifluoroacetic acid. Chromatography refers to column chromatography performed using 32-63 μm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to
5 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure implies the use of a rotary evaporator.

EXAMPLE 1

Preparation of B

10 9-[(BROMOACETYL)AMINO]ANHYDROTETRACYCLINE

9-Aminoanhydrotetracycline (prepared according to the procedure detailed in M. Menachery and M. Cava., "Amino Derivatives of Anhydrotetracyclines", Can. J. Chem., 62, 2583-2584 (1984)) (1.00 g, 2.09 mmol) was dissolved in 12 ml of 1-methyl-2-pyrrolidinone. Sodium bicarbonate (700 mg, 8.33 mmol) was added, followed by 220
15 μl of bromoacetyl bromide. The resulting reaction mixture was stirred at room temperature under an inert atmosphere of nitrogen. After 15 minutes, another 220 μl of bromoacetyl bromide was added. The resulting reaction mixture was stirred at room temperature for 90 minutes. It was then added dropwise to 300 ml of ice cold ether/isopropanol (10:1). The orange solids were collected by filtration and dried. This
20 material was redissolved in 200 ml of water. The pH of the reaction mixture was adjusted to 5. This aqueous mixture was then extracted with ethyl acetate. The combined ethyl acetate layers were dried (sodium sulfate) and concentrated under reduced pressure to give 520 mg of the product. ^1H NMR (dimethyl sulfoxide- d_6) 8.22 (d, 1H, J=9.1 Hz) 7.41 (d, 1H, J=9.1 Hz) 2.36 (s, 3H).

25

EXAMPLE 2

9-[(BROMOPROPIONYL)AMINO]ANHYDROTETRACYCLINE

In a procedure analogous to Example 1 except that 3-bromopropionyl-bromide was used instead of bromoacetyl bromide, the title compound was prepared.

EXAMPLE 3

30 9-[(PYRROLIDINOACETYL)AMINO]ANHYDROTETRACYCLINE

In a typical run, 100 mg of a compound from Example 1 was dissolved in 2 ml of anhydrous 1-methyl-2-pyrrolidinone. Pyrrolidine (0.75 ml) was added and the resulting reaction mixture was stirred at room temperature for 30 minutes. It was then

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added dropwise into 15 mL of ice cold ether/isopropanol (10:1). The resulting solids were collected by filtration and dried to give the desired product.

EXAMPLES 4-8

In a method analogous to Example 3 the compounds depicted in Table 1, Examples 4-8, were prepared.

EXAMPLE 9

9-(PHENYLUREA)ANHYDROTETRACYCLINE

9-Aminoanhydrotetracycline (300 mg, 0.628 mmol) was dissolved in 3 ml of 1-methyl-2-pyrrolidinone. Phenyl isocyanate (112 mg, 0.942 mmol) was added and the resulting reaction mixture was stirred at room temperature for 90 minutes. The reaction mixture was then added dropwise to 50 ml of ice cold ether/isopropanol (10:1). The orange solids were collected by filtration and dried to give 370 mg of the product.

EXAMPLE 10

9-[(METHOXYCARBONYL)AMINO]ANHYDROTETRACYCLINE

9-Aminoanhydrotetracycline (750 mg, 1.57 mmol) was dissolved in 5 ml of 1-methyl-2-pyrrolidinone. Sodium bicarbonate (NaHCO_3) (750 mg, 8.95 mmol) was added, followed by 0.3 ml of methyl chloroformate. The resulting reaction mixture was stirred at room temperature for 30 min. It was then added dropwise to 30 ml of ice cold ether/isopropanol (10:1). The orange solids were collected by filtration and dried. This material was redissolved in 50 ml of water and the pH was adjusted to 5. This aqueous mixture was then extracted with ethyl acetate (EtOAc). The combined organic layers were dried over sodium sulfate (Na_2SO_4), and concentrated under reduced pressure to give 120 mg of the product.

EXAMPLES 11-13, AND 16-17

In a method analogous to Example 10 the compounds of Examples 11-13, 16 and 17, depicted in Table 1, were prepared.

EXAMPLE 14

9-(ACETYL AMINO)ANHYDROTETRACYCLINE

9-Aminoanhydrotetracycline (1.0 g, 2.09 mmol) was dissolved in 16 ml of water. Sodium acetate (0.781 g, 9.52 mmol) was added and the resulting aqueous solution was cooled to approximately 0°C. Acetic anhydride (0.30 ml) was added at 0°C and

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the resulting reaction mixture was stirred at 0°C for 20 minutes. Concentrated ammonium hydroxide (0.16 ml) was then added and the resulting reaction mixture was stirred at 0°C for 5 minutes. The reaction mixture was warmed to room temperature and the pH was adjusted to 5 with dilute HCl. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give 980 mg of the title compound.

EXAMPLE 15

9-(FORMYLAMINO)ANHYDROTETRACYCLINE

9-Aminoanhydrotetracycline (500 mg, 1046 mmol) was dissolved in 8 ml of 96% formic acid along with 86 mg of sodium acetate. The reaction mixture was cooled in an ice bath and acetic anhydride (1.5 ml) was added dropwise. The resulting reaction mixture was stirred at 0°C for 10 minutes and then at room temperature for 1 hour. The reaction mixture was then added dropwise to 50 ml of ice cold diethyl ether/isopropanol (10:1). The solids were collected by filtration and then redissolved in water. The pH was adjusted to 5 and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give 350 mg of the title compound.

EXAMPLE 18

9-AMINO-7-CHLORO-6-DEMETHYLANHYDROTETRACYCLINE

7-Chloro-6-demethylanhydrotetracycline (2.3 g, 4.75 mmol) was dissolved in 200 ml of water. The reaction mixture was chilled in ice and sodium nitrite was added as a solution in water (393 mg sodium nitrite in 10 ml of water). The pH of the reaction mixture was adjusted to 1 with concentrated HCl. The reaction mixture was left standing in the refrigerator (at about 15°C) overnight. The following morning, the pH of the reaction mixture was adjusted to 9 with 5M sodium hydroxide. Sodium hydrosulfite (4.13 g) was added and the resulting reaction mixture was stirred at room temperature for 40 minutes. It was then extracted with ethyl acetate. The combined organic layers were dried (sodium sulfate), and concentrated under reduced pressure. The resulting residue was dissolved in 200 ml of methanol and 4 ml of concentrated HCl. The resulting solution was concentrated under reduced pressure to give 1.82 g of the title compound.

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EXAMPLE 19Preparation of E9-[(BROMOACETYL)AMINO]-7-CHLORO-6-DEMETHYLANHYDROTETRACYCLINE

In a method analogous to that used in Example 1 except 9-amino-7-chloro-6-demethylanhydrotetracycline is used as a starting material 9-[(bromoacetyl)amino]-7-chloro-6-demethylanhydrotetracycline was prepared.

EXAMPLE 209-[(PYRROLIDINOACETYL)AMINO]-7-CHLORO-6-DEMETHYLANHYDROTETRACYCLINE

In a typical run, 100 mg of a compound from Example 19 was dissolved in 2 ml of anhydrous 1-methyl-2-pyrrolidinone. Pyrrolidine (0.75 ml) was added and the resulting reaction mixture was stirred at room temperature for 30 minutes. It was then added dropwise into 15 mL of ice cold ether/isopropanol (10:1). The resulting solids were collected by filtration and dried to give the desired product.

EXAMPLES 21-389-SUBSTITUTED-7-CHLORO-6-DEMETHYLANHYDROTETRACYCLINES

In a method analogous to that used in Example 20, using the appropriate amine reagent, the 9-substituted-7-chloro-6-demethylanhydrotetracyclines were prepared.

EXAMPLE 399-AMINO-6-DEMETHYLANHYDROTETRACYCLINE

7-Chloro-6-demethylanhydrotetracycline (1.5 g, 3.09 mmol) was dissolved in 20 ml of 2-methoxyethanol. The resulting solution was transferred to a hydrogenation bottle. After 460 mg of 10% palladium on carbon (Pd on C), was added, the resulting reaction mixture was hydrogenated under 50 psi of hydrogen for 5 hours. The reaction mixture was then filtered through diatomaceous earth (Celite®) to remove the catalyst. The filtrate was concentrated under reduced pressure to a volume of approximately 10 ml. This solution was then added dropwise to 100 ml of ice cold ether/isopropanol (10:1). The bright yellow solids were collected by filtration and dried to give 1.14 g of 6-demethylanhydrotetracycline.

6-Demethylanhydrotetracycline (50 mg, 1.21 mmol) was dissolved in 40 ml of water. The aqueous solution was cooled in an ice bath and sodium nitrite (100 mg, 1.45 mmol) was added as a solution in 5 ml of water. The pH of the reaction mixture was adjusted to 1 with concentrated hydrochloric acid. The resulting reaction mixture

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was placed in the refrigeration (about 15°C) overnight. The following morning, the pH of the reaction mixture was adjusted to about 9 with 5 M sodium hydroxide (aq). An excess of sodium dithionite (1.05, 6.05 mmol) was added the resulting reaction mixture was stirred at room temperature for 30 minutes. (The pH was about 4.5). The aqueous
5 layer was then extracted with ethyl acetate. The combined organic layers were dried (sodium sulfate), and concentrated under reduced pressure. The resulting residue was redissolved in 10 ml of methanol and 1 ml of concentrated hydrochloric acid. This solution was concentrated under reduced pressure and dried under high vacuum to give 148 mg of 9-amino-6-demethylanhydrotetracycline.

10

EXAMPLE 40

9-[(BROMOACETYL)AMINO-6-DEMETHYLANHYDROTETRACYCLINE

9-Amino-6-demethylanhydrotetracycline (178 mg, 0.383 mmol) was dissolved 2 ml of 1-methyl-2-pyrrolidinone along with 168 mg of sodium bicarbonate. Bromoacetyl bromide (0.04 ml, 0.460 mmol) was added at room temperature. The resulting reaction
15 mixture was stirred at room temperature for 30 minutes. Another portion of bromoacetyl bromide (0.022 ml, 0.249 mmol) was added and the resulting reaction mixture was stirred at room temperature for another 2 hours. The reaction mixture was then diluted with 2 ml of methanol and filtered to remove the sodium bicarbonate₃. The filtrate was concentrated and then added dropwise to 10 ml of ice-cold
20 ether/isopropanol (10:1). The solids were collected by filtration and dried to give 200 mg of the crude product.

EXAMPLE 41

9-[(METHOXYCARBONYL)AMINO]TETRACYCLINE

In a typical case, 180 mg of compound from Example 10 was dissolved in 30
25 ml of CHCl₃, and 1 ml of methanol. 5, 10, 15, 20-Tetraphenyl -21H, 23H-porphine (TPP, 10mg) was added and the resulting reaction mixture was transferred to a Pyrex round-bottom flask that was equipped with an oxygen gas inlet and vent. This Pyrex flask was placed 2-3 inches from a 450-watt, medium-pressure, mercury vapor lamp from Ace-Hanovia. This lamp, in turn, was positioned vertically inside a borosilicate
30 photochemical immersion well that was equipped with a Pyrex absorption sleeve. The immersion well was cooled with running tap water; and the extra voltage that was required for the lamp was provided by a power supply box from Ace-Hanovia. This entire set up was placed inside the appropriate photochemical chamber. To initiate the

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singlet oxygen photooxidation, oxygen was bubbled through the reaction mixture while it was irradiated with the 450-watt mercury vapor lamp. After 15 minutes, the lamp was turned off and the oxygen was disconnected. The reaction mixture was concentrated under reduced pressure. The resulting residue was taken up in 20 ml of methanol and
5 filtered to remove the TPP. The filtrate, containing the peroxide intermediate was used for the next step without further purification.

The peroxide intermediate prepared above, was placed in a hydrogenation bottle. Platinum oxide (36 mg) was added and the resulting reaction mixture was hydrogenated under 50 psi of hydrogen for 2 hours. The reaction mixture was then
10 filtered through Celite® to remove the catalyst and the filtrate was concentrated under reduced pressure. The resulting residue was redissolved in 2 ml of methanol and then added dropwise to 15 ml of ice cold ether/isopropanol (10:1). The light tan solids were collected by filtration and dried to give 70 mg of the product.

¹H NMR (dimethyl sulfoxide-d₆): 7.85 (d, 1H, J:8.4 Hz); 7.10 (d, 1H, J:8.4 Hz);
15 1.51 (s, 3H).

MS (LSIMS, m+1) 518.

EXAMPLE 42-45

In a method analogous to Example 41, except that the compounds prepared in Examples 10, 11, 12, 14 and 15 were respectively used instead, the 9-substituted
20 tetracyclines were prepared.

EXAMPLE 46

9-[(N,N-DIMETHYLAMINO ACETYL)AMINO]TETRACYCLINE

In a typical run, 500 mg of the anhydrotetracycline intermediate B (Example 1) was dissolved in 50 mL of CHCl₃ and 2 ml of methanol. 5, 10, 15, 20-Tetraphenyl-21H, 23H-porphine (TPP, 10 mg) was added and the resulting reaction mixture was
25 transferred to a Pyrex round-bottom flask that was equipped with an oxygen gas inlet and vent. This Pyrex flask was placed 2-3 inches from a 450-watt, medium-pressure, mercury vapor lamp from Ace-Hanovia. This lamp, in turn, was positioned vertically inside a borosilicate photochemical immersion well that was equipped with a Pyrex
30 absorption sleeve. The immersion well was cooled with running tap water; and the extra voltage that was required for the lamp was provided by a power supply box from Ace-Hanovia. This entire set up was placed inside the appropriate photochemical chamber. To initiate the singlet oxygen photooxidation, oxygen was bubbled through the

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reaction mixture while it was irradiated with the 450-watt mercury vapor lamp. After 15 minutes, the lamp was turned off and the oxygen was disconnected. The reaction mixture was concentrated under reduced pressure. The resulting residue was taken up in 30 ml of methanol and filtered to remove the TPP. The filtrate, containing the
5 peroxide intermediate was used for the next step without further purification.

^1H NMR (dimethyl sulfoxide- d_6) 8.26 (d, 1H, $J = 8.9$ Hz), 7.24 (d, 1H, $J = 8.9$ Hz), 1.55 (s, 3H).

The peroxide intermediate, prepared above, was transferred to a hydrogenation bottle. 5% Rhodium on carbon (120 mg) was added and the resulting reaction mixture
10 was hydrogenated under 50 psi of hydrogen for 5 minutes at room temperature. The reaction mixture was filtered through diatomaceous earth to remove the catalyst. The filtrate was concentrated under reduced pressure to give 380 mg of 9-[(bromoacetyl)-amino]dehydrotetracycline.

^1H NMR (dimethyl sulfoxide- d_6) 8.26 (d, 1H, $J = 8.2$ Hz), 7.24 (d, 1H, $J = 8.2$
15 Hz), 1.55 (s, 3H).

9-[(Bromoacetyl)amino]dehydrotetracycline (320 mg) was dissolved in 4 ml of the 40% solution of dimethylamine in water and 1 mL of methanol. The resulting reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was then concentrated under reduced pressure. The resulting residue was redissolved
20 in 5 ml of methanol and added dropwise to 30 ml of ice cold ether/isopropanol (10:1). The brown solids were collected by filtration and dried to give 319 mg of the free base of the dehydrotetracycline.

^1H NMR (dimethyl sulfoxide- d_6) 8.17 (d, 1H, $J = 8.3$ Hz), 6.85 (d, 1H, $J = 8.3$ Hz), 1.37 (s, 3H). MS (LSIMS, $m+1$) = 543.

25 This material was converted to the hydrochloride salt by dissolution in 10 ml of methanol followed by addition of 2 equivalents of 1N aqueous hydrochloric acid.

^1H NMR (dimethyl sulfoxide- d_6) 8.10 (d, 1H, $J = 8.3$ Hz), 7.32 (d, 1H, $J = 8.3$ Hz), 1.60 (s, 3H).

The solution containing the hydrochloride salt of the dehydrotetracycline
30 (prepared above) was transferred to a hydrogenation bottle. Platinum oxide (52 mg) was added and the resulting reaction mixture was hydrogenated under 50 psi of hydrogen for 2 hours at room temperature. The reaction mixture was filtered through

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Celite®. The filtrate was concentrated under reduced pressure and dried under high vacuum to obtain 202 mg of the title compound.

¹H NMR (dimethyl sulfoxide-d₆) 8.10 (d, 1H, J = 8.2 Hz), 7.13 (d, 1H, J = 8.2 Hz), 1.52 (s, 3H). MS (LSIMS, m+1) = 545. Analytically pure sample was obtained by
5 preparative HPLC.

EXAMPLE 47

9-[(t-BUTYLAMINOACETYL)AMINO]TETRACYCLINE

9-[(Bromoacetyl)amino]dehydrotetracycline, from Example 46, (340 mg, 0.604 mmol) was dissolved in 3 ml of anhydrous acetonitrile and 1 ml of 1-methyl-2-
10 pyrrolidinone. t-Butylamine (0.25 ml, 2.42 mmol) was added and the resulting reaction mixture was stirred at room temperature for 40 minutes. The reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in 3 ml of methanol and added dropwise to 15 ml of ice cold ether/isopropanol (10:1). The brown
15 solids were collected by filtration and dried to give 280 mg of 9-[(t-butylaminoacetyl)amino]dehydrotetracycline. Some of this material (250 mg) was converted to the hydrochloride salt by dissolving it in 10 ml of methanol followed by addition of two equivalents of 1N aqueous hydrochloric acid.

A solution containing 150 mg of the hydrochloride salt of the dehydrotetracycline in 10 ml of methanol was transferred to a hydrogenation bottle. Platinum oxide (30 mg)
20 was added and the resulting reaction mixture was hydrogenated under 50 psi of hydrogen for 2 hours at room temperature. The reaction mixture was filtered through Celite® to remove the catalyst. The filtrate was concentrated to a volume of about 4 ml. This was then added dropwise to 15 ml of ice cold ether/isopropanol (10:1). The light
tan solids were collected by filtration and dried to give 110 mg of the title compound.

25 ¹H NMR (dimethyl sulfoxide-d₆) 8.25 (d, 1H, J = 8.3 Hz), 7.18 (d, 1H, J = 8.3 Hz), 1.55 (s, 3H), 1.29 (s, 9H). MS (LSIMS, m+1) = 574. An analytically pure sample was obtained by preparative HPLC.

EXAMPLES 48-52 AND 54-63

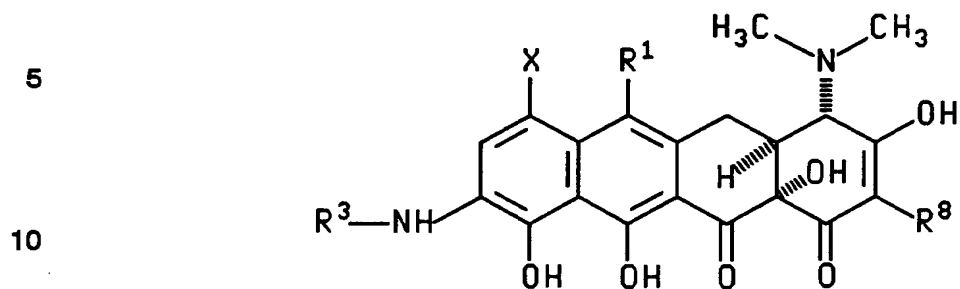
In a method analogous to Example 47, except that the appropriate amine
30 reagent was used, the 9-substituted tetracyclines of Examples 48-52 and 54-63 were prepared.

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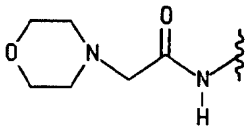
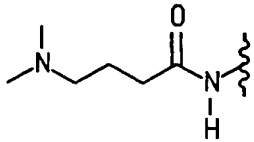
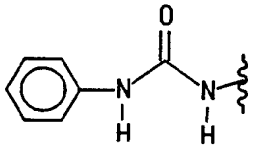
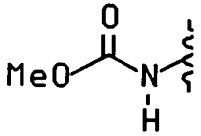
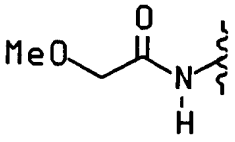
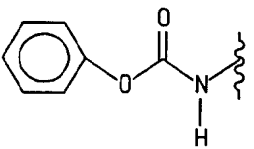
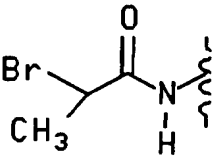
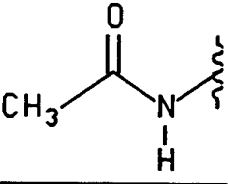
EXAMPLE 53**9-(METHYLAMINOACETYLAMINO)TETRACYCLINE**

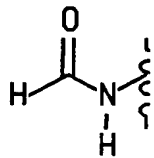
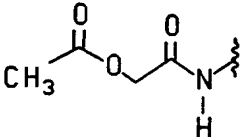
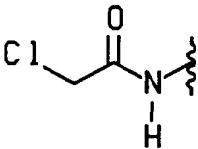
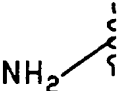
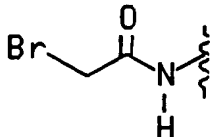
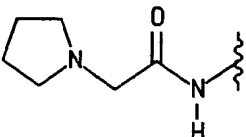
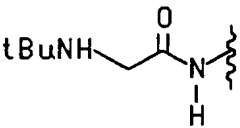
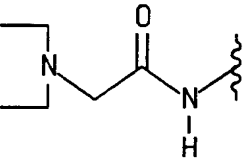
In a method analogous to Example 46 except that 40% methylamine in water was used instead of 40% dimethylamine in water, the title compound was prepared.

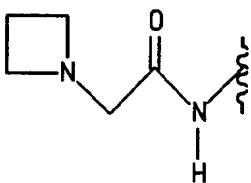
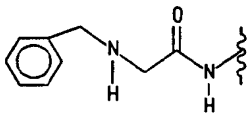
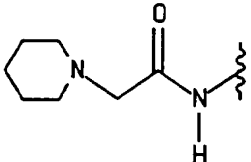
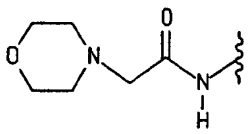
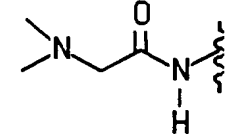
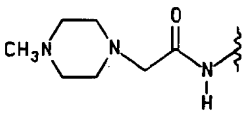
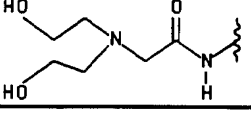
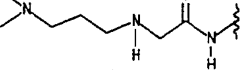
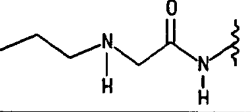
TABLE 1



15	Example No.	R^3-NH	X	R^1	R^8	MS(LSIMS) (m+1)
	1		H	CH ₃	CONH ₂	(m-Br)=482
	2		H	CH ₃	CONH ₂	NT
	3		H	CH ₃	CONH ₂	553
	4		H	CH ₃	CONH ₂	527
	5		H	CH ₃	CONH ₂	555
20	6		H	CH ₃	CONH ₂	589

Example No.	R^3-NH	X	R^1	R^8	MS(LSIMS) (m+1)
7		H	CH ₃	CONH ₂	569
8		H	CH ₃	CONH ₂	555
9		H	CH ₃	CONH ₂	561
10		H	CH ₃	CONH ₂	449
11		H	CH ₃	CONH ₂	514
12		H	CH ₃	CONH ₂	562
13		H	CH ₃	CONH ₂	N.T.
14		H	CH ₃	CONH ₂	483

Example No.	R^3-NH	X	R^1	R^2	MS(LSIMS) (m+1)
15		H	CH ₃	CONH ₂	469
16		H	CH ₃	CONH ₂	542
17		H	CH ₃	CONH ₂	517
18		Cl	H	CONH ₂	498
19		Cl	H	CONH ₂	502 (m+Br)
20		Cl	H	CONH ₂	573
21		Cl	H	CONH ₂	611
22		Cl	H	CONH ₂	575

Example No.	R^3-NH	X	R^1	R^8	MS(LSIMS) (m+1)
23		Cl	H	CONH ₂	559
24		Cl	H	CONH ₂	609
25		Cl	H	CONH ₂	587
26		Cl	H	CONH ₂	589
27		Cl	H	CONH ₂	547
28		Cl	H	CONH ₂	602
29		Cl	H	CONH ₂	607
30		Cl	H	CONH ₂	604
31		Cl	H	CONH ₂	561

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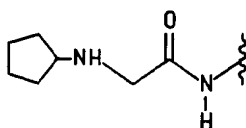
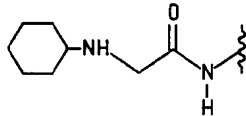
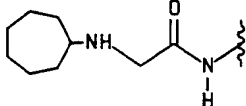
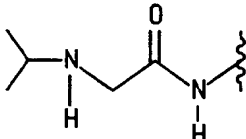
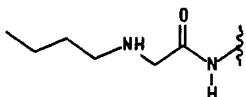
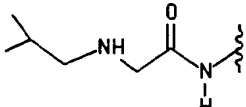
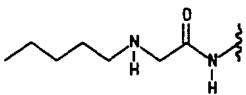

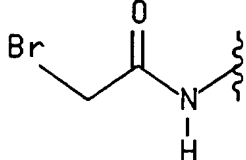
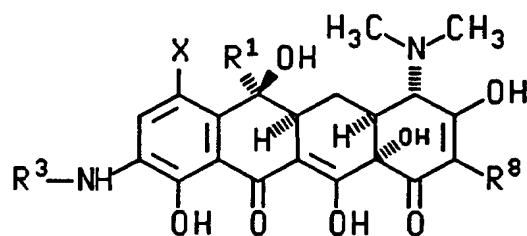
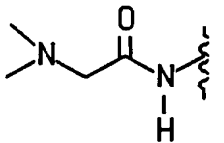
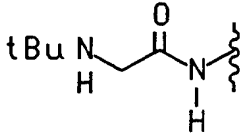
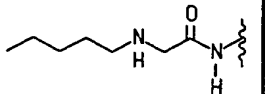
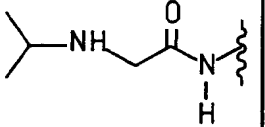
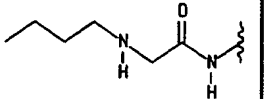
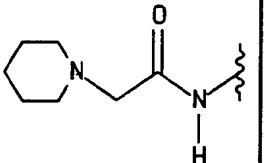
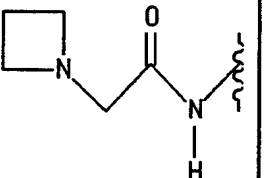
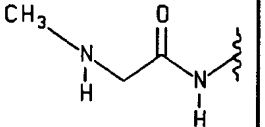
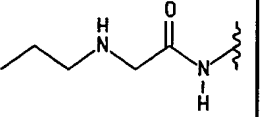
Example No.	R^3-NH 	X	R^1	R^8	MS(LSIMS) (m+1)
32		Cl	H	CONH ₂	587
33		Cl	H	CONH ₂	601
34		Cl	H	CONH ₂	615
35		Cl	H	CONH ₂	561
36		Cl	H	CONH ₂	575
37		Cl	H	CONH ₂	575
38		Cl	H	CONH ₂	589
39	H_2N 	H	H	CONH ₂	427
40		H	H	CONH ₂	467 (m+-Br)

TABLE 2

Example No.	R^3-NH	X	R^1	R^8	MS(LSIMS) (m+1)
41		H	CH ₃	CONH ₂	518
42		H	CH ₃	CONH ₂	487
43		H	CH ₃	CONH ₂	532
44		H	CH ₃	CONH ₂	580
45		H	CH ₃	CONH ₂	502

Example No.	R^3-NH	X	R^1	R^8	MS(LSIMS) (m+1)
46		H	CH ₃	CONH ₂	545
47		H	CH ₃	CONH ₂	574
48		H	CH ₃	CONH ₂	587
49		H	CH ₃	CONH ₂	559
50		H	CH ₃	CONH ₂	573
51		H	CH ₃	CONH ₂	585
52		H	CH ₃	CONH ₂	557
53		H	CH ₃	CONH ₂	530
54		H	H ₃	CONH ₂	559

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Example No.	R^3-NH	X	R^1	R^6	MS(LSIMS) (m+1)
55		H	CH ₃	CONH ₂	571
56		H	CH ₃	CONH ₂	599
57		H	CH ₃	CONH ₂	587
58		H	CH ₃	CONH ₂	587
59		H	CH ₃	CONH ₂	613
60		H	CH ₃	CONH ₂	603
61		H	CH ₃	CONH ₂	603
62		H	CH ₃	CONH ₂	602
63		H	CH ₃	CONH ₂	573

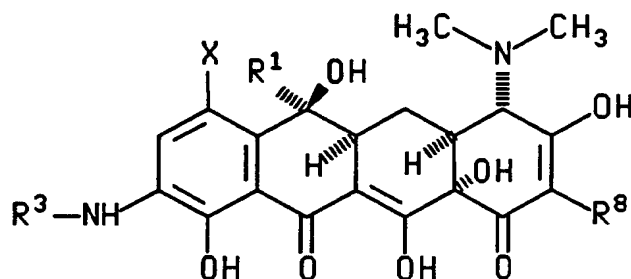
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CLAIMS

1. A compound of the formula

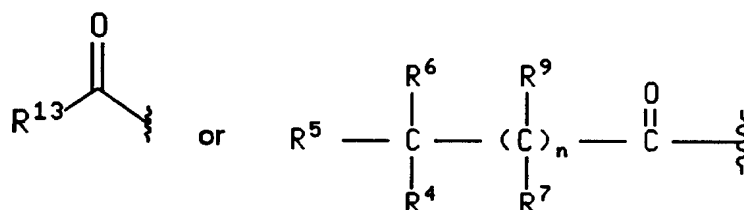


I

wherein X is hydrogen;

R¹ is methyl;

R³ is a group of the formula



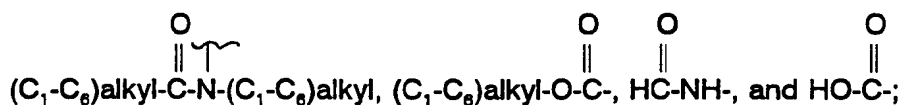
wherein n is an integer from zero to four;

R⁴ is hydrogen or (C₁-C₆)alkyl;

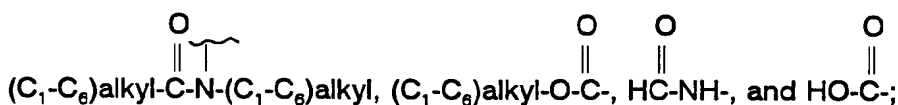
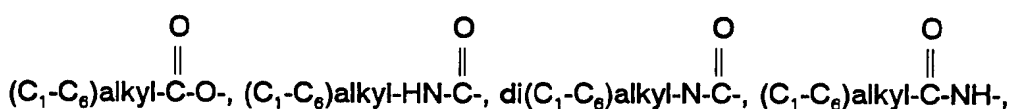
R⁵ is hydrogen; (C₁-C₆)alkyl optionally substituted with one or more substituents, preferably one to three substituents, independently selected from methylthio, (C₁-C₆)alkoxy, amino, guanidino, amido, carboxamido,

(C₁-C₆)alkyl-C(=O)-O-, (C₁-C₆)alkyl-HN-C(=O)-, di(C₁-C₆)alkyl-N-C(=O)-, (C₁-C₆)alkyl-C(=O)-NH-,

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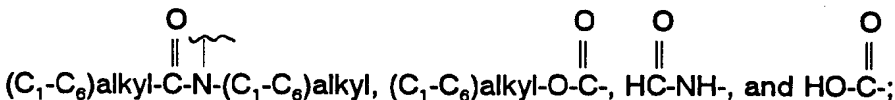
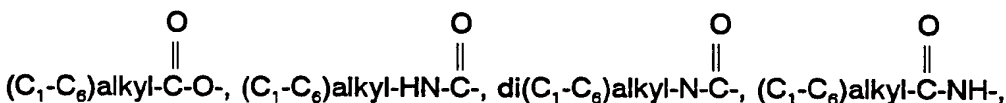


(C₆-C₁₀)aryl-(CH₂)_h-, wherein h is an integer from zero to three, wherein the (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl-(CH₂)_h group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



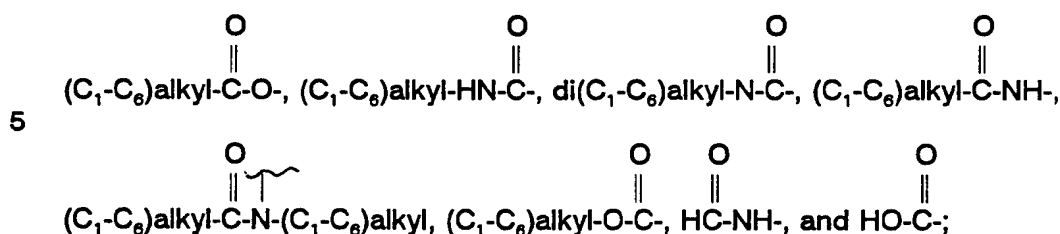
or (C₃-C₆)cycloalkyl-(CH₂)_j-, wherein j is an integer from zero to three, wherein the (C₃-C₆)cycloalkyl moiety of said (C₃-C₆)cycloalkyl-(CH₂)_j- group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-

C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

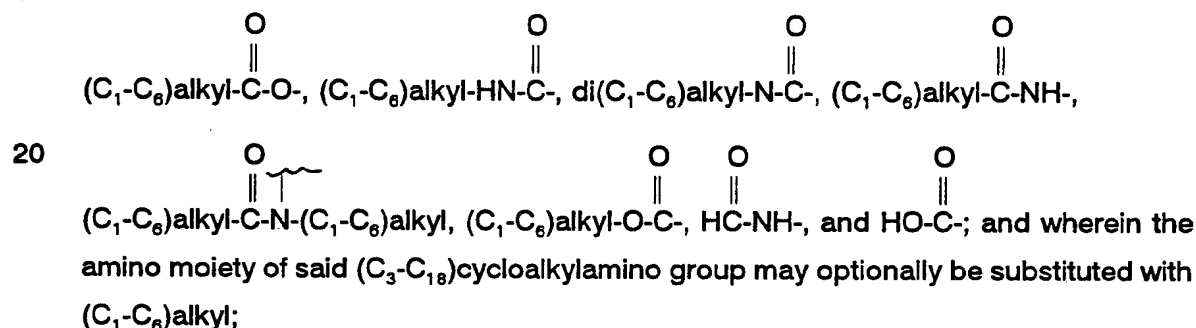


R⁶ is halogen; amino; hydroxylamino; (C₁-C₁₂)alkylamino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

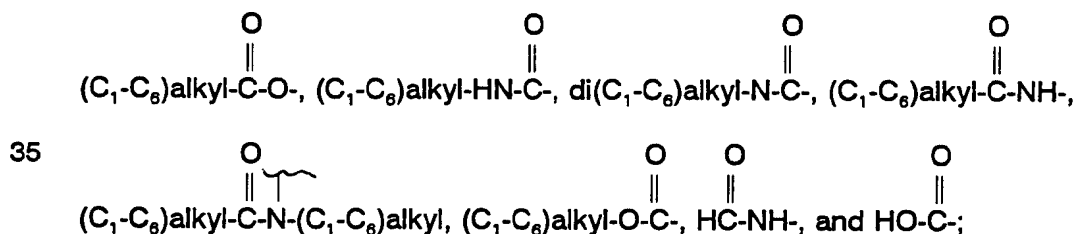
-70-



(C₃-C₁₈)cycloalkylamino wherein the (C₃-C₁₈)cycloalkyl moiety of said (C₃-C₁₈)cycloalkyl amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido, (C₁-C₆)alkyl,



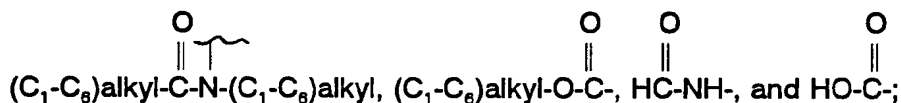
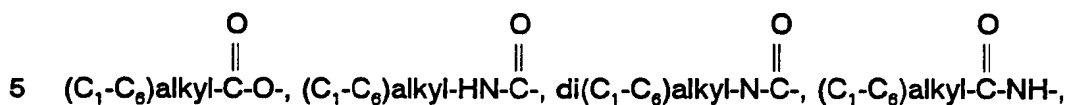
25 di(C₃-C₁₈)cycloalkyl-amino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido, (C₁-C₆)alkyl,



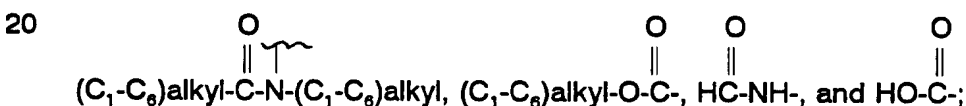
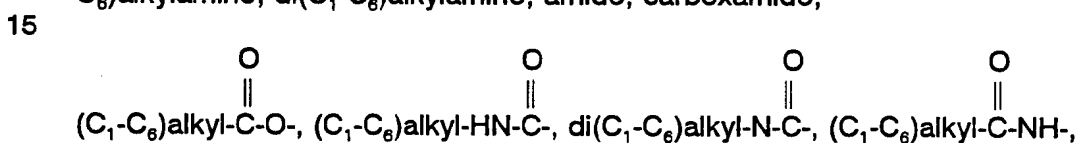
(C₆-C₁₀)aryl-(CH₂)_m-amino, wherein m is an integer from zero to three, wherein the (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl-(CH₂)_m-amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido,

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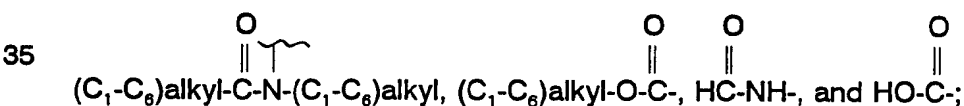
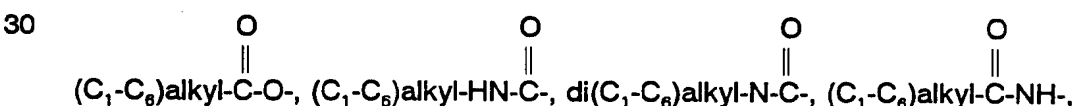
carboxamido, (C₁-C₆)alkyl,



10 di(C₁-C₆)alkyl-amino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



(C₂-C₁₀)azacycloalkyl optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

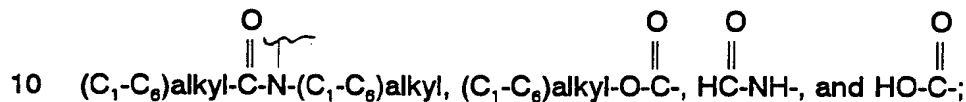
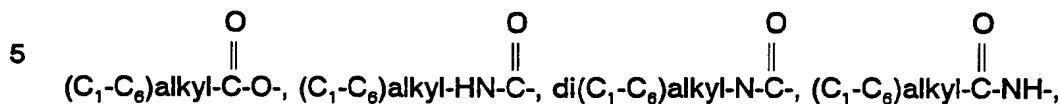


40 carboxy(C₁-C₆)alkylamino; (C₁-C₆)alkyl-O-C(=O)-amino; (C₁-C₆)alkyl-O-C(=O)-(C₁-C₆)alkylamino; (C₁-C₆)alkoxyamino; (C₃-C₈)cycloalkoxyamino;

(C₆-C₁₀)aryl-(CH₂)_t-oxyamino, wherein t is an integer from zero to three, wherein the (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl-(CH₂)_t-oxyamino group may optionally be substituted with one or more substituents, preferably one to three substituents,

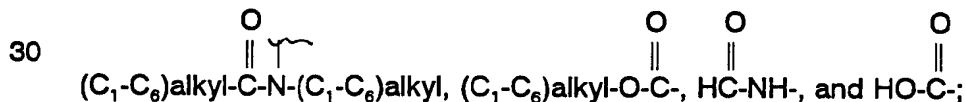
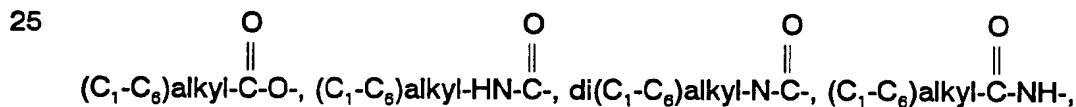
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independently selected from halogen, (C₁-C₆)alkoxy, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, di(C₁-C₆)alkylamino, amido, carboxamido,



or a heterocycle-(CH₂)_k-amino group, wherein k is an integer from zero to three, wherein said heterocycle is selected from pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, 15 pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalyl, quinazolinyl, cinnolinyl and benzoxazinyl;

20 wherein the heterocycle moiety of said heterocycle-(CH₂)_k- group may be, where possible, substituted with from one to three substituents independently selected from (C₁-C₆)alkyl, halogen, hydroxy, cyano, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



or R⁵ and R⁶ taken together may form a -(CH₂)_pW(CH₂)_q- ring wherein W is

35 selected from $\tilde{N}(C_1-C_3)alkyl-, \overset{\sim}{CH}_2-, \overset{\sim}{NH}, O, S, \text{ and } \overset{\sim}{NOB};$ wherein B is selected from hydrogen and (C₁-C₃)alkyl, p is an integer from one to three, and q is an integer from one to three;

R⁷ is hydrogen or (C₁-C₆)alkyl;

R⁸ is -CONH₂ or -CONHCH₂-NR¹¹R¹²;

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R^8 is hydrogen or (C_1-C_6) alkyl;

R^{11} is (C_1-C_6) alkyl;

R^{12} is (C_1-C_6) alkyl; or

5 R^{11} and R^{12} taken together form a $-(CH_2)_r-Y-(CH_2)_s$ ring wherein Y is $-N-(C_1-$

$C_3)$ alkyl, $-CH_2-$, $-NH$, oxygen, sulfur or $-NOB$; wherein B is selected from hydrogen or (C_1-C_3) alkyl, r is an integer from one to three, and s is an integer from one to three;

10 R^{13} is hydrogen, (C_1-C_6) alkoxy- (C_1-C_6) alkyl, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkylmethyl, or (C_6-C_{10}) aryl optionally substituted with one or more substituents, preferably one to three substituents, independently selected from fluoro, hydroxy, (C_1-C_6) alkoxy, trihalo (C_1-C_6) alkyl, amino, cyano, (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, amido, carboxamido,

15

(C_1-C_6) alkyl-C(=O)-O-, (C_1-C_6) alkyl-HN-C(=O)-, di (C_1-C_6) alkyl-N-C(=O)-, (C_1-C_6) alkyl-C(=O)-NH-,

20

(C_1-C_6) alkyl-C(=O)-N-(C_1-C_6)alkyl, (C_1-C_6) alkyl-O-C(=O)-, HC-NH-C(=O)-, and HO-C(=O)-;

and the pharmacologically acceptable organic and inorganic salts or metal complexes.

25

2. A compound according to claim 1 wherein X is hydrogen, R^1 is methyl, and R^8 is $-CONH_2$.

3. A compound according to claim 2 wherein n is zero; R^4 is hydrogen; and R^5 is hydrogen.

4. A compound according to claim 3 wherein R^6 is halogen, amino, hydroxylamino, (C_1-C_{12}) alkylamino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C_1-C_6) alkoxy, (C_1-C_6) alkylsulfonyl, trihalo (C_1-C_6) alkyl, amino, cyano, $(C_1-$

35

$C_6)$ alkylamino, di (C_1-C_6) alkylamino, amido, carboxamido,
 (C_1-C_6) alkyl-C(=O)-O-, (C_1-C_6) alkyl-HN-C(=O)-, di (C_1-C_6) alkyl-N-C(=O)-, (C_1-C_6) alkyl-C(=O)-NH-,

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$\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-N-(C}_1\text{-C}_6\text{)alkyl, } (\text{C}_1\text{-C}_6\text{)alkyl-O-C-}, \text{HC-NH-}, \text{and HO-C-;} \end{array}$

5 $(\text{C}_3\text{-C}_{18})\text{cycloalkylamino}$ wherein the $(\text{C}_3\text{-C}_{18})\text{cycloalkyl}$ moiety of said $(\text{C}_3\text{-C}_{18})\text{cycloalkyl amino}$ group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, $(\text{C}_1\text{-C}_6)\text{alkylsulfonyl}$, trihalo $(\text{C}_1\text{-C}_6)\text{alkyl}$, amino, cyano, $(\text{C}_1\text{-C}_6)\text{alkylamino}$, di $(\text{C}_1\text{-C}_6)\text{alkylamino}$, amido, carboxamido, $(\text{C}_1\text{-C}_6)\text{alkyl}$,

10 $\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-O-}, (\text{C}_1\text{-C}_6)\text{alkyl-HN-C-}, \text{di}(\text{C}_1\text{-C}_6)\text{alkyl-N-C-}, (\text{C}_1\text{-C}_6)\text{alkyl-C-NH-}, \end{array}$

15 $\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-N-(C}_1\text{-C}_6\text{)alkyl, } (\text{C}_1\text{-C}_6\text{)alkyl-O-C-}, \text{HC-NH-}, \text{and HO-C-;} \end{array}$ and wherein the amino moiety of said $(\text{C}_3\text{-C}_{18})\text{cycloalkyl amino}$ group may optionally be substituted with $(\text{C}_1\text{-C}_6)\text{alkyl}$;

20 di $(\text{C}_1\text{-C}_6)\text{alkyl-amino}$ optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, $(\text{C}_1\text{-C}_6)\text{alkylsulfonyl}$, trihalo $(\text{C}_1\text{-C}_6)\text{alkyl}$, amino, cyano, $(\text{C}_1\text{-C}_6)\text{alkylamino}$, di $(\text{C}_1\text{-C}_6)\text{alkylamino}$, amido, carboxamido,

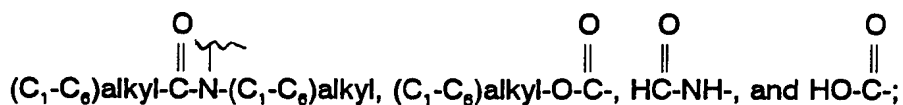
25 $\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-O-}, (\text{C}_1\text{-C}_6)\text{alkyl-HN-C-}, \text{di}(\text{C}_1\text{-C}_6)\text{alkyl-N-C-}, (\text{C}_1\text{-C}_6)\text{alkyl-C-NH-}, \end{array}$

30 $\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-N-(C}_1\text{-C}_6\text{)alkyl, } (\text{C}_1\text{-C}_6\text{)alkyl-O-C-}, \text{HC-NH-}, \text{and HO-C-;} \end{array}$

35 $(\text{C}_2\text{-C}_{10})\text{azacycloalkyl}$ optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, $(\text{C}_1\text{-C}_6)\text{alkylsulfonyl}$, trihalo $(\text{C}_1\text{-C}_6)\text{alkyl}$, amino, cyano, $(\text{C}_1\text{-C}_6)\text{alkylamino}$, di $(\text{C}_1\text{-C}_6)\text{alkylamino}$, amido, carboxamido,

40 $\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-O-}, (\text{C}_1\text{-C}_6)\text{alkyl-HN-C-}, \text{di}(\text{C}_1\text{-C}_6)\text{alkyl-N-C-}, (\text{C}_1\text{-C}_6)\text{alkyl-C-NH-}, \end{array}$

-75-



5

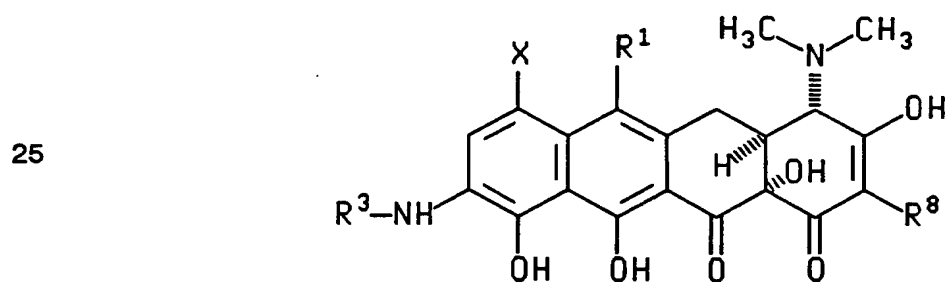
or R⁵ and R⁶ taken together may form a $-(\text{CH}_2)_p\text{W}(\text{CH}_2)_q-$ ring wherein W is

selected from $-\overset{\text{~}}{\text{N}}(C_1-C_3)\text{alkyl}-\text{CH}_2-$, $-\overset{\text{~}}{\text{NH}}$, O, S, and $-\text{NOB}$; wherein B is selected from
 10 hydrogen and $(C_1-C_3)\text{alkyl}$, p is an integer from one to three, and q is an integer from
 one to three.

5. A compound according to claim 4 wherein said compound is selected from:

- 9-[(N,N-dimethylaminoacetyl)amino]tetracycline;
 15 9-[(tert-butylaminoacetyl)amino]tetracycline;
 9-[(N-methyl-N'-tert-butylaminoacetyl)amino]tetracycline;
 9-[(diisopropylaminoacetyl)amino]tetracycline;
 9-[(pyrrolidinoacetyl)amino]tetracycline;
 9-[(cycloheptylaminoacetyl)amino]tetracycline; and
 20 9-[(tert-amylaminoacetyl)amino]tetracycline.

6. A compound of the formula



30

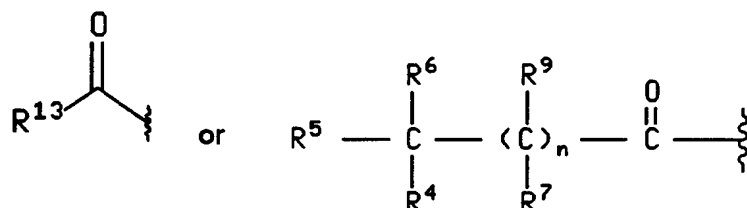
I I

wherein X is hydrogen or chlorine;

R¹ is H or CH₃;

R³ is a group of the formula

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wherein n is an integer from zero to four;

R⁴ is hydrogen or (C₁-C₆)alkyl;

R⁵ is hydrogen; (C₁-C₆)alkyl optionally substituted with one or more
 5 substituents, preferably one to three substituents, independently selected from
 methylthio, (C₁-C₆)alkoxy, amino, guanidino, amido, carboxamido,

10 $\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-\text{O}-, (\text{C}_1-\text{C}_6)\text{alkyl}-\text{HN}-\text{C}-, \text{di}(\text{C}_1-\text{C}_6)\text{alkyl}-\text{N}-\text{C}-, (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-\text{NH}-, \end{array}$

15 $\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-\text{N}-\text{C}-\text{N}-(\text{C}_1-\text{C}_6)\text{alkyl}, (\text{C}_1-\text{C}_6)\text{alkyl}-\text{O}-\text{C}-, \text{HC}-\text{NH}-, \text{and HO}-\text{C}-; \end{array}$

(C₆-C₁₀)aryl-(CH₂)_h-, wherein h is an integer from zero to three, wherein the (C₆-
 C₁₀)aryl moiety of said (C₆-C₁₀)aryl-(CH₂)_h group may optionally be substituted with one
 or more substituents, preferably one to three substituents, independently selected from
 20 halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl,
 amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

25 $\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-\text{O}-, (\text{C}_1-\text{C}_6)\text{alkyl}-\text{HN}-\text{C}-, \text{di}(\text{C}_1-\text{C}_6)\text{alkyl}-\text{N}-\text{C}-, (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-\text{NH}-, \end{array}$

$\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1-\text{C}_6)\text{alkyl}-\text{C}-\text{N}-\text{C}-\text{N}-(\text{C}_1-\text{C}_6)\text{alkyl}, (\text{C}_1-\text{C}_6)\text{alkyl}-\text{O}-\text{C}-, \text{HC}-\text{NH}-, \text{and HO}-\text{C}-; \end{array}$

30 or (C₃-C₆)cycloalkyl-(CH₂)_j-, wherein j is an integer from zero to three, wherein
 the (C₃-C₆)cycloalkyl moiety of said (C₃-C₆)cycloalkyl-(CH₂)_j- group may optionally be
 substituted with one or more substituents, preferably one to three substituents,
 independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-

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C_6)alkylsulfonyl, trihalo(C_1 - C_6)alkyl, amino, cyano, (C_1 - C_6)alkylamino, di(C_1 - C_6)alkylamino, amido, carboxamido,

5

$(C_1-C_6)alkyl-C(=O)-O-$, $(C_1-C_6)alkyl-HN-C(=O)-$, $di(C_1-C_6)alkyl-N-C(=O)-$, $(C_1-C_6)alkyl-C(=O)-NH-$,

10

$(C_1-C_6)alkyl-C(=O)-N-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-O-C(=O)-$, $HC-NH-$, and $HO-C(=O)-$;

R^6 is halogen; amino; hydroxylamino; (C_1 - C_{12})alkylamino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C_1 - C_6)alkoxy, (C_1 - C_6)alkylsulfonyl, trihalo(C_1 - C_6)alkyl, amino, cyano, (C_1 - C_6)alkylamino, di(C_1 - C_6)alkylamino, amido, carboxamido,

20 $(C_1-C_6)alkyl-C(=O)-O-$, $(C_1-C_6)alkyl-HN-C(=O)-$, $di(C_1-C_6)alkyl-N-C(=O)-$, $(C_1-C_6)alkyl-C(=O)-NH-$,

$(C_1-C_6)alkyl-C(=O)-N-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-O-C(=O)-$, $HC-NH-$, and $HO-C(=O)-$;

25

(C_3 - C_{18})cycloalkylamino wherein the (C_3 - C_{18})cycloalkyl moiety of said (C_3 - C_{18})cycloalkyl amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C_1 - C_6)alkoxy, (C_1 - C_6)alkylsulfonyl, trihalo(C_1 - C_6)alkyl, amino, cyano,

30 (C_1 - C_6)alkylamino, di(C_1 - C_6)alkylamino, amido, carboxamido, (C_1 - C_6)alkyl,

35 $(C_1-C_6)alkyl-C(=O)-O-$, $(C_1-C_6)alkyl-HN-C(=O)-$, $di(C_1-C_6)alkyl-N-C(=O)-$, $(C_1-C_6)alkyl-C(=O)-NH-$,

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$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-N-(C}_1\text{-C}_6)\text{alkyl} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-O-C-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ \text{HC-NH-} \end{array}, \text{ and } \begin{array}{c} \text{O} \\ \parallel \\ \text{HO-C-} \end{array};$$
 and wherein the amino moiety of said (C₃-C₁₈)cycloalkylamino group may optionally be substituted with
 5 (C₁-C₆)alkyl;

di(C₃-C₁₈)cycloalkyl-amino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino,
 10 di(C₁-C₆)alkylamino, amido, carboxamido, (C₁-C₆)alkyl,

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-O-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-HN-C-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ \text{di(C}_1\text{-C}_6)\text{alkyl-N-C-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-NH-} \end{array},$$
 15

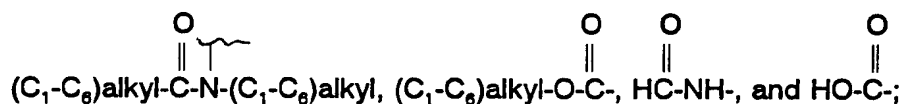
$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-N-(C}_1\text{-C}_6)\text{alkyl} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-O-C-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ \text{HC-NH-} \end{array}, \text{ and } \begin{array}{c} \text{O} \\ \parallel \\ \text{HO-C-} \end{array};$$
 (C₆-C₁₀)aryl-(CH₂)_m-amino, wherein m is an integer from zero to three, wherein
 20 the (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl-(CH₂)_m-amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido,
 25 carboxamido, (C₁-C₆)alkyl,

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-O-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-HN-C-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ \text{di(C}_1\text{-C}_6)\text{alkyl-N-C-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-NH-} \end{array},$$
 30

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-N-(C}_1\text{-C}_6)\text{alkyl} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-O-C-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ \text{HC-NH-} \end{array}, \text{ and } \begin{array}{c} \text{O} \\ \parallel \\ \text{HO-C-} \end{array};$$
 di(C₁-C₆)alkyl-amino optionally substituted with one or more substituents,
 35 preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

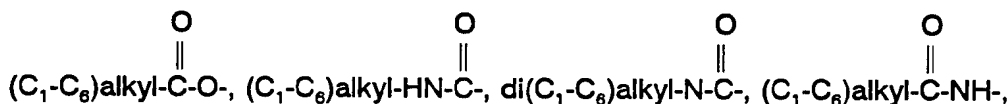
$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-O-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-HN-C-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ \text{di(C}_1\text{-C}_6)\text{alkyl-N-C-} \end{array}, \begin{array}{c} \text{O} \\ \parallel \\ (\text{C}_1\text{-C}_6)\text{alkyl-C-NH-} \end{array},$$
 40

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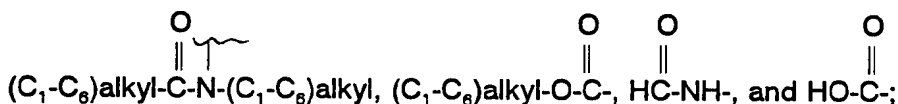


(C₂-C₁₀)azacycloalkyl optionally substituted with one or more substituents,
 5 preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-
 C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano,
 (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

10



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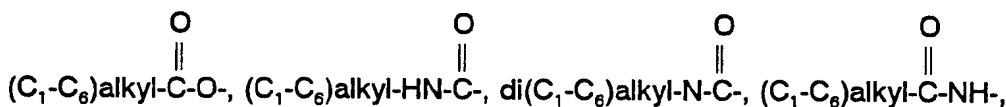


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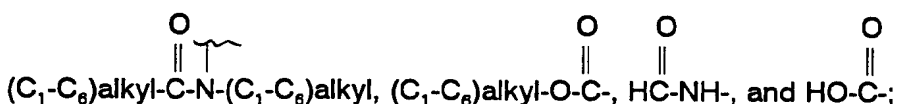
carboxy(C₁-C₆)alkylamino; (C₁-C₆)alkyl-O-C(=O)-amino; (C₁-C₆)alkyl-O-C(=O)-(C₁-
 C₆)alkylamino; (C₁-C₆)alkoxyamino; (C₃-C₈)cycloalkoxyamino;

(C₆-C₁₀)aryl-(CH₂)_t-oxyamino, wherein t is an integer from zero to three, wherein
 the (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl-(CH₂)_t-oxyamino group may optionally be
 25 substituted with one or more substituents, preferably one to three substituents,
 independently selected from halogen, (C₁-C₆)alkoxy, trihalo(C₁-C₆)alkyl, amino, cyano,
 (C₁-C₆)alkylamino, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, di(C₁-C₆)alkylamino,
 amido, carboxamido,

30



35



or a heterocycle-(CH₂)_k-amino group, wherein k is an integer from zero to three,
 wherein said heterocycle is selected from pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl,
 imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-
 oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl,
 40 pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 1,2,5-
 oxathiazinyl, 1,2,6-oxathiazinyl, benzoxazolyl, benzothiazolyl, benzisothiazolyl,

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benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalyl, quinazolinyl, cinnolinyl and benzoxazinyl;

wherein the heterocycle moiety of said heterocycle-(CH₂)_k- group may be, where
 5 possible, substituted with from one to three substituents independently selected from (C₁-C₆)alkyl, halogen, hydroxy, cyano, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

10 (C₁-C₆)alkyl-C(=O)-O-, (C₁-C₆)alkyl-HN-C(=O)-, di(C₁-C₆)alkyl-N-C(=O)-, (C₁-C₆)alkyl-C(=O)-NH-,

15 (C₁-C₆)alkyl-C(=O)-N-(C₁-C₆)alkyl, (C₁-C₆)alkyl-O-C(=O)-, HC-NH-C(=O)-, and HO-C(=O)-;

or R⁵ and R⁶ taken together may form a -(CH₂)_pW(CH₂)_q- ring wherein W is

selected from $\begin{array}{c} \sim \\ | \\ -N(C_1-C_3)alkyl, -CH_2-, -NH, O, S, \text{ and } -NOB; \end{array}$ wherein B is selected from
 20 hydrogen and (C₁-C₃)alkyl, p is an integer from one to three, and q is an integer from one to three;

R⁷ is hydrogen or (C₁-C₆)alkyl;

R⁸ is -CONH₂ or -CONHCH₂-NR¹¹R¹²;

R⁹ is hydrogen or (C₁-C₆)alkyl;

25 R¹¹ is (C₁-C₆)alkyl;

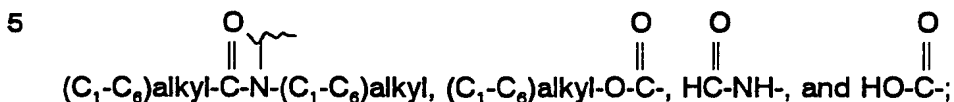
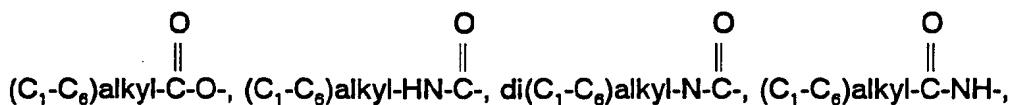
R¹² is (C₁-C₆)alkyl; or

R¹¹ and R¹² taken together form a $\begin{array}{c} \sim \\ | \\ -(CH_2)_r-Y-(CH_2)_s \end{array}$ ring wherein Y is $\begin{array}{c} \sim \\ | \\ -N-(C_1- \end{array}$

30 C₃)alkyl, $\begin{array}{c} \sim \\ | \\ -CH_2-, -NH, \text{ oxygen, sulfur or } -NOB; \end{array}$ wherein B is selected from hydrogen or (C₁-C₃)alkyl, r is an integer from one to three, and s is an integer from one to three;

R¹³ is hydrogen, (C₁-C₆)alkoxy-(C₁-C₆)alkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkylmethyl, or (C₆-C₁₀)aryl optionally substituted with one or
 35 more substituents, preferably one to three substituents, independently selected from fluoro, hydroxy, (C₁-C₆)alkoxy, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

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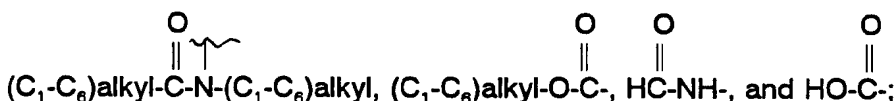
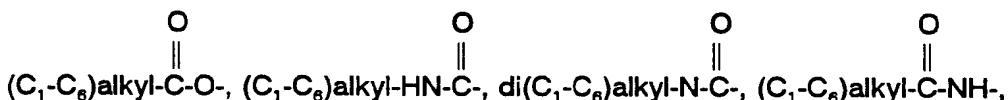


and the pharmacologically acceptable organic and inorganic salts or metal complexes.

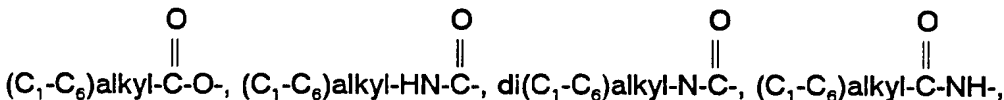
10 7. A compound according to claim 6 wherein X is hydrogen, R¹ is methyl, and R⁸ is -CONH₂.

8. A compound according to claim 7 wherein n is zero; R⁴ is hydrogen; and R⁵ is hydrogen.

9. A compound according to claim 8 wherein R⁶ is halogen, amino, hydroxylamino, (C₁-C₁₂)alkylamino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



(C₃-C₁₈)cycloalkylamino wherein the (C₃-C₁₈)cycloalkyl moiety of said (C₃-C₁₈)cycloalkyl amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido, (C₁-C₆)alkyl,



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$(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-N-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-O-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl$, $HC-\overset{\overset{O}{\parallel}}{N}-$, and $HO-\overset{\overset{O}{\parallel}}{C}-$; and wherein the amino moiety of said $(C_3-C_{18})cycloalkyl$ amino group may optionally be substituted with
 5 $(C_1-C_6)alkyl$;

$di(C_1-C_6)alkyl-amino$ optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, $(C_1-C_6)alkylsulfonyl$, trihalo $(C_1-C_6)alkyl$, amino, cyano, $(C_1-C_6)alkylamino$, $di(C_1-C_6)alkylamino$, amido, carboxamido,

$(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-O-$, $(C_1-C_6)alkyl-HN-\overset{\overset{O}{\parallel}}{C}-$, $di(C_1-C_6)alkyl-N-\overset{\overset{O}{\parallel}}{C}-$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-NH-$,

$(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-N-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-O-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl$, $HC-\overset{\overset{O}{\parallel}}{N}-$, and $HO-\overset{\overset{O}{\parallel}}{C}-$;

$(C_2-C_{10})azacycloalkyl$ optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy$, $(C_1-C_6)alkylsulfonyl$, trihalo $(C_1-C_6)alkyl$, amino, cyano, $(C_1-C_6)alkylamino$, $di(C_1-C_6)alkylamino$, amido, carboxamido,

$(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-O-$, $(C_1-C_6)alkyl-HN-\overset{\overset{O}{\parallel}}{C}-$, $di(C_1-C_6)alkyl-N-\overset{\overset{O}{\parallel}}{C}-$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-NH-$,

$(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-N-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl$, $(C_1-C_6)alkyl-\overset{\overset{O}{\parallel}}{C}-O-\overset{\overset{O}{\parallel}}{C}-(C_1-C_6)alkyl$, $HC-\overset{\overset{O}{\parallel}}{N}-$, and $HO-\overset{\overset{O}{\parallel}}{C}-$;

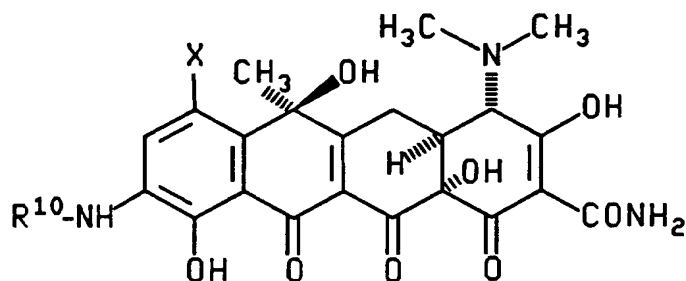
or R^5 and R^6 taken together may form a $-(CH_2)_pW(CH_2)_q-$ ring wherein W is

selected from $-\overset{\overset{O}{\parallel}}{N}(C_1-C_3)alkyl-$, $-CH_2-$, $-NH-$, O, S, and $-NOB$; wherein B is selected from hydrogen and $(C_1-C_3)alkyl$, p is an integer from one to three, and q is an integer from one to three.

10. A compound of the formula

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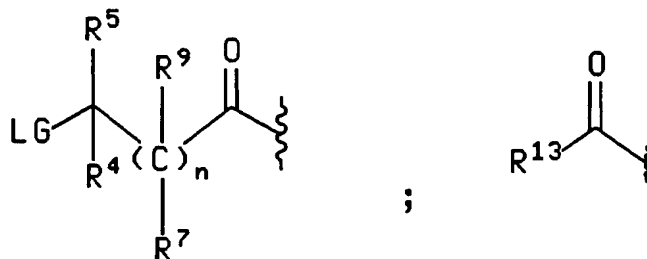


III

10 wherein X is hydrogen;

R¹⁰ is a group of the formula

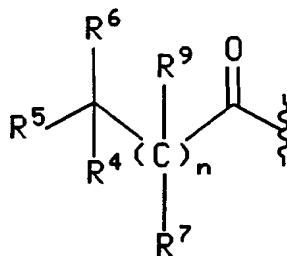
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;

or

20



25

wherein n is an integer from zero to four;

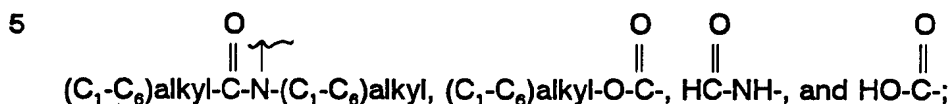
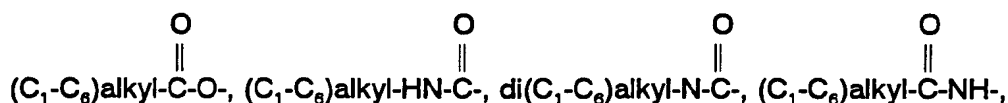
LG is chloro, bromo, iodo, -OSO₂Ph, -OSO₂PhCH₃, -OSO₂CH₃, or -OSO₂CF₃;

30

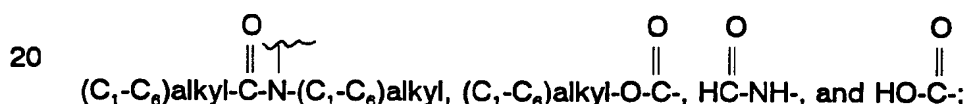
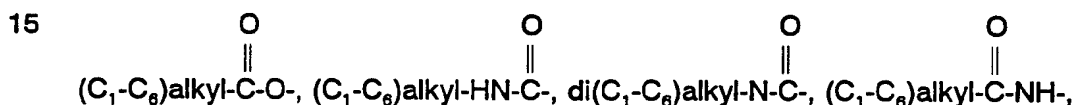
R⁴ is hydrogen or (C₁-C₆)alkyl;

R⁵ is hydrogen; (C₁-C₆)alkyl optionally substituted with one or more substituents, preferably one to three substituents, independently selected from methylthio, (C₁-C₆)alkoxy, amino, guanidino, amido, carboxamido,

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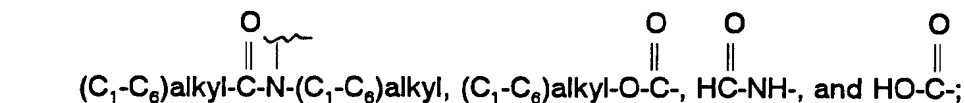
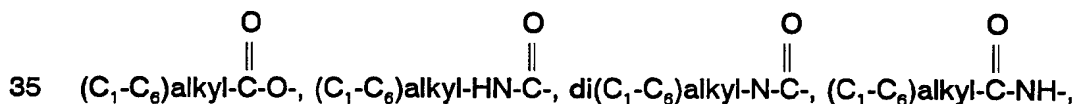


(C₆-C₁₀)aryl-(CH₂)_h-, wherein h is an integer from zero to three, wherein the (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl-(CH₂)_h group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



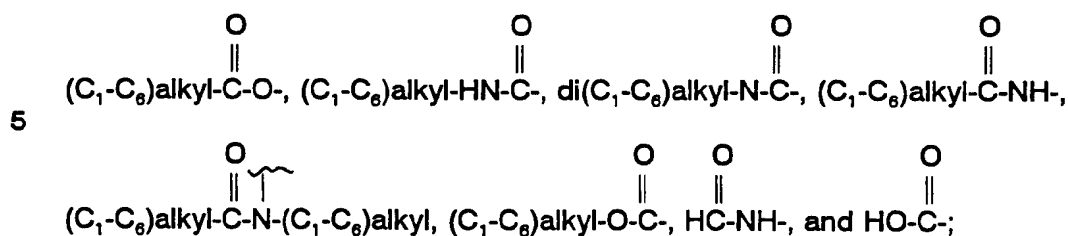
or (C₃-C₆)cycloalkyl-(CH₂)_j-, wherein j is an integer from zero to three, wherein the (C₃-C₆)cycloalkyl moiety of said (C₃-C₆)cycloalkyl-(CH₂)_j- group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-

30 (C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

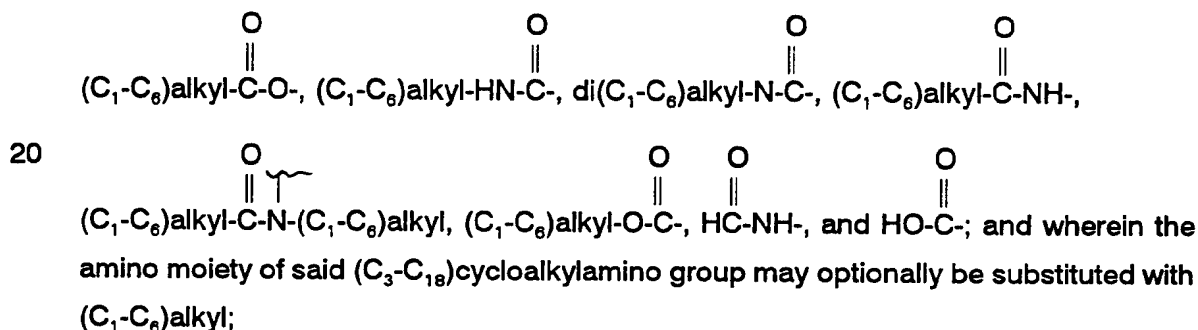


R⁶ is halogen; amino; hydroxylamino; (C₁-C₁₂)alkylamino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

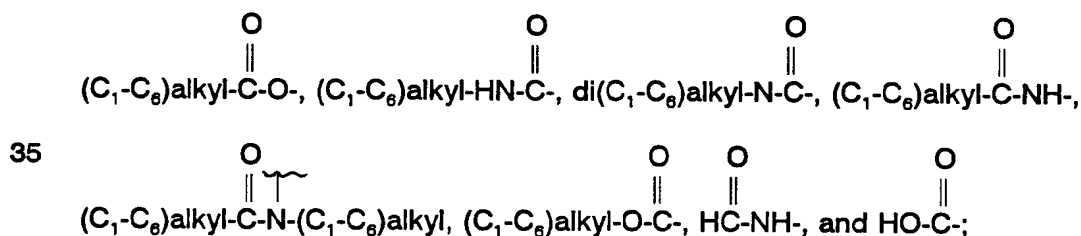
-85-



(C₃-C₁₈)cycloalkylamino wherein the (C₃-C₁₈)cycloalkyl moiety of said (C₃-C₁₈)cycloalkyl amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido, (C₁-C₆)alkyl,



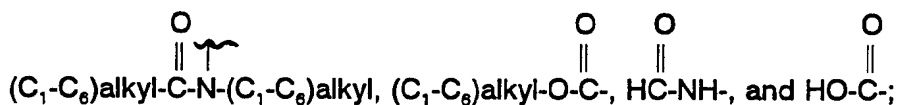
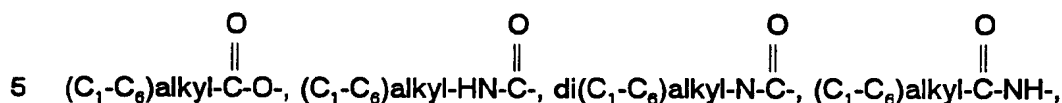
25 di(C₃-C₁₈)cycloalkyl-amino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido, (C₁-C₆)alkyl,



(C₆-C₁₀)aryl-(CH₂)_m-amino, wherein m is an integer from zero to three, wherein the (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl-(CH₂)_m-amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido,

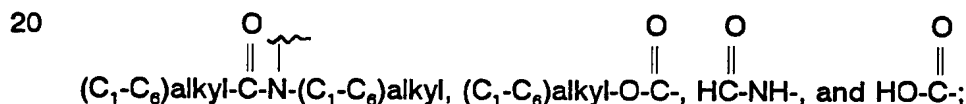
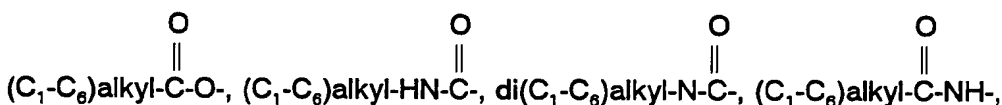
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-86-

carboxamido, (C₁-C₆)alkyl,

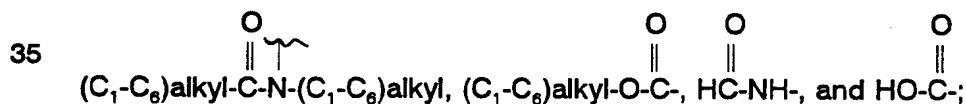
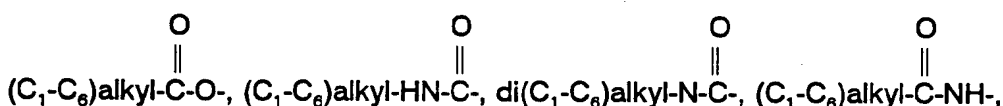
10 di(C₁-C₆)alkyl-amino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-

15 C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



(C₂-C₁₀)azacycloalkyl optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano,

25 (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,

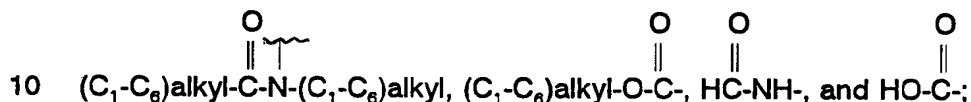
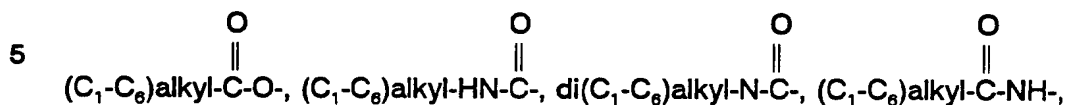


40 carboxy(C₁-C₆)alkylamino; (C₁-C₆)alkyl-O-C-amino; (C₁-C₆)alkyl-O-C-(C₁-C₆)alkylamino; (C₁-C₆)alkoxyamino; (C₃-C₈)cycloalkoxyamino;

(C₆-C₁₀)aryl-(CH₂)_t-oxyamino, wherein t is an integer from zero to three, wherein the (C₆-C₁₀)aryl moiety of said (C₆-C₁₀)aryl-(CH₂)_t-oxyamino group may optionally be substituted with one or more substituents, preferably one to three substituents,

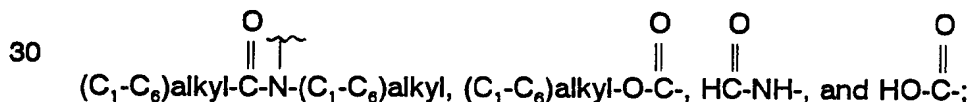
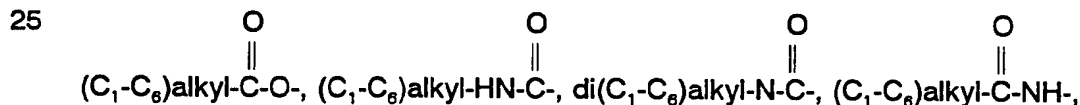
-87-

independently selected from halogen, (C₁-C₆)alkoxy, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, di(C₁-C₆)alkylamino, amido, carboxamido,



or a heterocycle-(CH₂)_k-amino group, wherein k is an integer from zero to three, wherein said heterocycle is selected from pyrrolyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1,3,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,5-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, 15 pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, 1,2,5-thiadiazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, benzoxazolyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofuranyl, isobenzofuranyl, chromenyl, isoindolyl, indolyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxalyl, quinazolinyl, cinnolyl and benzoxazinyl;

20 wherein the heterocycle moiety of said heterocycle-(CH₂)_k- group may be, where possible, substituted with from one to three substituents independently selected from (C₁-C₆)alkyl, halogen, hydroxy, cyano, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



or R⁵ and R⁶ taken together may form a -(CH₂)_pW(CH₂)_q- ring wherein W is

35 selected from $\begin{array}{ccc} \sim & \sim & \sim \\ | & | & | \\ -\text{N}(\text{C}_1\text{-C}_3)\text{alkyl-}, & -\text{CH}_2\text{-}, & -\text{NH-}, \end{array}$ O, S, and -NOB; wherein B is selected from hydrogen and (C₁-C₃)alkyl, p is an integer from one to three, and q is an integer from one to three;

R⁷ is hydrogen or (C₁-C₆)alkyl;

R⁸ is -CONH₂ or -CONHCH₂-NR¹¹R¹²;

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R^9 is hydrogen or (C_1-C_6) alkyl;

R^{11} is (C_1-C_6) alkyl;

R^{12} is (C_1-C_6) alkyl; or

5 R^{11} and R^{12} taken together form a $-(CH_2)_r-Y-(CH_2)_s$ ring wherein Y is $-N-(C_1-$

$C_3)$ alkyl, $-CH_2-$, $-NH$, oxygen, sulfur or $-NOB$; wherein B is selected from hydrogen or (C_1-C_3) alkyl, r is an integer from one to three, and s is an integer from one to three;

10 R^{13} is hydrogen, (C_1-C_6) alkoxy- (C_1-C_6) alkyl, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkylmethyl, or (C_6-C_{10}) aryl optionally substituted with one or more substituents, preferably one to three substituents, independently selected from fluoro, hydroxy, (C_1-C_6) alkoxy, trihalo (C_1-C_6) alkyl, amino, cyano, (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, amido, carboxamido,

15 (C_1-C_6) alkyl-C(=O)-O-, (C_1-C_6) alkyl-HN-C(=O)-, di (C_1-C_6) alkyl-N-C(=O)-, (C_1-C_6) alkyl-C(=O)-NH-,

20 (C_1-C_6) alkyl-C(=O)-N-(C(=O)- (C_1-C_6) alkyl), (C_1-C_6) alkyl-O-C(=O)-, HC-NH-C(=O)-, and HO-C(=O)-;

and the pharmacologically acceptable organic and inorganic salts or metal complexes.

25 11. A compound according to claim 10 wherein X is hydrogen, R^1 is methyl, and R^9 is $-CONH_2$.

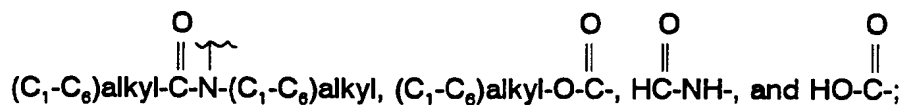
12. A compound according to claim 11 wherein n is zero; R^4 is hydrogen; and R^5 is hydrogen.

30 13. A compound according to claim 12 wherein R^6 is halogen, amino, hydroxylamino, (C_1-C_{12}) alkylamino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C_1-C_6) alkoxy, (C_1-C_6) alkylsulfonyl, trihalo (C_1-C_6) alkyl, amino, cyano, $(C_1-$

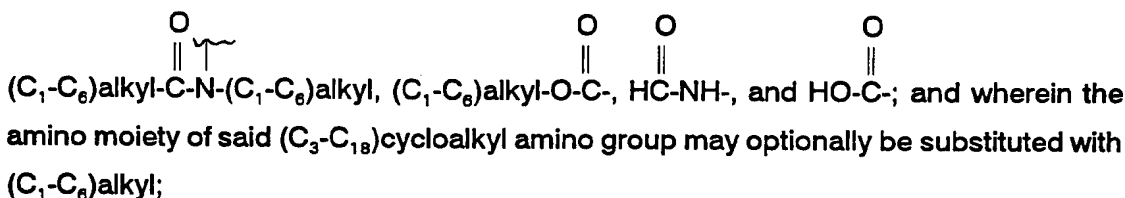
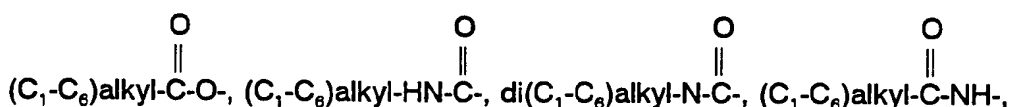
$C_6)$ alkylamino, di (C_1-C_6) alkylamino, amido, carboxamido,

35 (C_1-C_6) alkyl-C(=O)-O-, (C_1-C_6) alkyl-HN-C(=O)-, di (C_1-C_6) alkyl-N-C(=O)-, (C_1-C_6) alkyl-C(=O)-NH-,

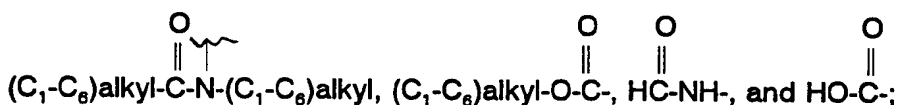
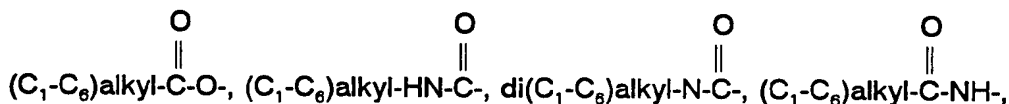
-89-



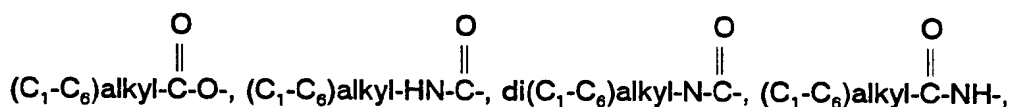
(C₃-C₁₈)cycloalkylamino wherein the (C₃-C₁₈)cycloalkyl moiety of said (C₃-C₁₈)cycloalkyl amino group may optionally be substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido, (C₁-C₆)alkyl,



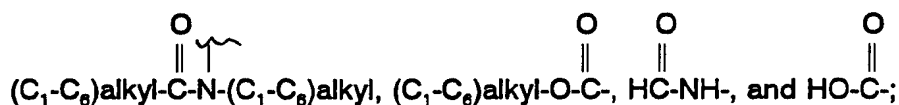
di(C₁-C₆)alkyl-amino optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



(C₂-C₁₀)azacycloalkyl optionally substituted with one or more substituents, preferably one to three substituents, independently selected from halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylsulfonyl, trihalo(C₁-C₆)alkyl, amino, cyano, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, amido, carboxamido,



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5 or R⁵ and R⁶ taken together may form a $-(\text{CH}_2)_p\text{W}(\text{CH}_2)_q-$ ring wherein W is

selected from $-\overset{\text{O}}{\parallel}\text{N}-(C_1-C_3)\text{alkyl}-$, $-\text{CH}_2-$, $-\text{NH}-$, O, S, and $-\text{NOB}-$; wherein B is selected from hydrogen and $(C_1-C_3)\text{alkyl}$, p is an integer from one to three, and q is an integer from
 10 one to three.

14. A method for the prevention, treatment or control of bacterial infections in a warm-blooded animal which comprises administering to said animal a pharmacologically effective amount of a compound according to claim 1.

15 15. A pharmaceutical composition for the prevention, treatment or control of bacterial infections in a warm-blooded animal which comprises a pharmacologically effective amount of a compound according to claim 1 in association with a pharmaceutically acceptable carrier.

16. A method for the prevention, treatment or control of bacterial infections in a warm-blooded animal which comprises administering to said animal a
 20 pharmacologically effective amount of a compound according to claim 6.

17. A pharmaceutical composition for the prevention, treatment or control of bacterial infections in a warm-blooded animal which comprises a pharmacologically effective amount of a compound according to claim 6 in association with a pharmaceutically acceptable carrier.

25 18. A method for treating or preventing osteoarthritis in a mammal which comprises administering to said animal a pharmacologically effective amount of a compound according to claim 1.

19. A pharmaceutical composition for treating or preventing osteoarthritis in a mammal, which comprises a pharmacologically effective amount of a compound
 30 according to claim 1 in association with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/IB 96/00335

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07C237/28 C07D295/14 C07C275/32 C07C271/30 C07C271/58 C07D205/04 A61K31/65		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D C07C A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. MED. CHEM., vol. 37, 1994, pages 184-188, XP002007660 SUM ET AL.: "Glycylcyclines. 1. A New Generation ..." see the whole document ---	1-5, 10-15, 18,19
Y	J. MED. CHEM., vol. 37, 1994, pages 3205-3211, XP002007661 BARDEN ET AL.: "Glycylcyclines. 3. 9-Aminodoxycyclinecarboxamides" see the whole document ---	1-5, 10-15, 18,19
Y	EP 0 618 190 A (AMERICAN CYANAMID CO) 5 October 1994 cited in the application see the whole document ---	1-5, 10-16, 18,19
-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
5 July 1996		04.10.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Steendijk, M

INTERNATIONAL SEARCH REPORT

Int. .onal Application No

PCT/IB 96/00335

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 582 789 A (AMERICAN CYANAMID CO) 16 February 1994 see the whole document ---	1-5, 10-16, 18,19
Y	EP 0 582 829 A (AMERICAN CYANAMID CO) 16 February 1994 see the whole document ---	1-5, 10-16, 18,19
Y	US 4 666 897 A (GOLUB LORNE M ET AL) 19 May 1987 see the whole document -----	18,19

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 96/00335

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Compounds of formula I, intermediates thereof of formula III and applications thereof (Claims 1-5, 10-15, 18 and 19)
2. Compounds of formula II and applications thereof (Claims 6-9, 16 and 17)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-5, 10-15, 18 and 19

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 96/00335

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0618190	05-10-94	US-A- 5371076 CA-A- 2120374 JP-A- 7138220	06-12-94 03-10-94 30-05-95
EP-A-0582789	16-02-94	US-A- 5420272 AU-A- 4461393 CA-A- 2103838 CN-A- 1087626 CZ-A- 9301616 FI-A- 933564 HU-A- 67691 HU-A- 67630 JP-A- 7309823 NO-A- 932871 NZ-A- 248356 PL-A- 300062 SK-A- 86293 US-A- 5386041 US-A- 5457096 US-A- 5495032 ZA-A- 9305893	30-05-95 17-02-94 14-02-94 08-06-94 16-03-94 14-02-94 28-04-95 28-04-95 28-11-95 14-02-94 21-12-95 21-02-94 11-05-94 31-01-95 10-10-95 27-02-96 09-03-94
EP-A-0582829	16-02-94	US-A- 5442059 AU-A- 4461193 CA-A- 2103845 CN-A- 1087899 CZ-A- 9301574 FI-A- 933568 HU-A, B 71594 HU-A- 66660 JP-A- 6199758 NO-A- 932873 NZ-A- 248342 PL-A- 300068 SK-A- 84893 US-A- 5495030 ZA-A- 9305890	15-08-95 17-02-94 14-02-94 15-06-94 16-03-94 14-02-94 29-01-96 28-12-94 19-07-94 14-02-94 26-07-95 21-02-94 08-06-94 27-02-96 11-03-94
US-A-4666897	19-05-87	US-A- 4935412 US-A- 4935411	19-06-90 19-06-90

Information on patent family members

PCT/IB 96/00335

Publication date